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Panel Meeting

August 5, 2003

PMA 030004 - Onyx® Liquid Embolic System for Treatment of Brain Arteriovenous Malformations

Sponsor: **Micro Therapeutics, Inc.**
2 Goodyear
Irvine, CA 92618

1. GENERAL INFORMATION

1.1. Device Generic Name

Artificial Embolization Device (21 CFR 882.5950)

Medical Specialty: Neurology, Product Code MFE, Class III

1.2. Device Trade Name

Onyx® Liquid Embolic System (Onyx® LES):

a) Onyx® 18 (6% EVOH, Model 105-7100-060)
b) Onyx® 34 (8% EVOH, Model 105-7100-080)

1.3. Intended Use

The Onyx® LES is an artificial embolization device intended for use in the treatment of brain arteriovenous malformations, when embolization is indicated to minimize blood loss or to reduce the BAVM size prior to surgery or radiosurgery.

1.4. Sponsor / Manufacturer Name and Address

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5. BACKGROUND

5.1. Overview of Disease State

Cerebral arteriovenous malformations (AVMs) are observed when there is an abnormal development between the arteries and veins. Normally, blood flows from the arteries to the veins via a capillary bed, but AVMs are missing this capillary bed. AVMs develop as an abnormal tangle of vessels (nidus) where the arteries are directly connected to the veins. Without the existence of the capillary bed, whose role is to dampen the high pressure as blood flows from the arteries to the veins, blood is allowed to flow across at high pressure. This high pressure through the veins causes them to dilate and may continue to hemorrhage.

AVMs have been theorized to develop during the early stages of life and don't typically become symptomatic for the patients until between 20 and 50 years of age[1]. Three out of every 10,000 persons are thought to have an AVM. About 50% of malformations present with intracranial hemorrhage, and 25% with partial seizures and epilepsy[2]. The remaining 25% present in the form of migraine headaches, focal or general neurological deficits, and cranial nerve dysfunctions. The annual incidence of intracranial hemorrhage due to arteriovenous malformations is between 1 and 3 per 100,000[1].

There are currently several approaches to treating AVMs including microsurgery, radiosurgery, and endovascular embolization in combination with micro- or radiosurgery. Microsurgery uses bipolar cauterization and surgical clips to remove the arterial feeders and retain the transit artery. The advantages of microsurgery are: 1) The procedure can remove the total AVM abnormality during the procedure; 2) it has a long proven track record; and 3) it can be used to treat small and large AVMs. The disadvantages of microsurgery are: 1) it is invasive, requiring a craniotomy; 2) the patient is placed under general anesthesia for the surgical procedure; and 3) certain deep intracranial AVMs cannot be treated. Results discussed by Deruty et al.[3] demonstrated that for lesions of all sizes, a "favorable" outcome can be expected from microsurgical resection in 81% to 95% of the patients. The mortality rate from surgical procedures varies from 1% to 14%[3].

Radiosurgery, unlike microsurgery, involves an intense targeted radiation that induces endothelial damage, subendothelial deposition of collagen, and proliferation of vascular

[1] Lawton MT, Spetzer RF. Surgical management of acutely ruptured arteriovenous malformations. In: Welch KMA, Caplan LR, Reis DJ, Siesjo BK, Weir B, eds. Primer on cerebrovascular diseases. San Diego, Academic Press, 1997, 511-519

[2] Cheung RTF. Management of intracranial vascular malformations – a neurologist's perspective. Clinical Review, Medical Progress October 2002

[3] Deruty R, Pelissou-Guyotat I, Mottolese C, Bascoulergue Y, Amat.D. The combined management of cerebral arteriovenous malformations. Experience with 100 cases and review of the literature. Acta Neurochir 1993; 123: 101-112.

smooth muscle in the vessels, leading to eventual obliteration of the malformation [4,5]. The advantages of radiosurgery are that it does not require a craniotomy and it allows for treatment of some small deep lesions that cannot be treated by microsurgery. The disadvantages of radiosurgery are: 1) typically lesions larger than 2.5 cm are not treated effectively; 2) there is an increased possibility of hemorrhage post procedure; and 3) there exists a risk of injuring adjacent brain tissue [6]. Total obliteration rates of AVMs have been reported to be greater than 80% with the gamma knife[7], particle beam, and linear accelerator techniques for lesions with a diameter under 1–3 cm[8,9]. The complication rates for radiosurgery cannot accurately be compared to microsurgery and/or embolization procedures due to delayed events (e.g., radiation-induced necrosis, and vascular changes) associated with this treatment.

Endovascular embolization involves the use of catheters to deliver a variety of occlusive agents such as permanent balloons, sclerosing drugs, thrombosing coils and rapidly acting glues. The advantages to performing an embolization procedure are: 1) no craniotomy is required; 2) can treat deep AVMs by treating small areas at a time and allowing the surrounding brain tissue to recover; and 3) the area to be treated can be tested prior to determine the reaction of the area before permanent treatment occurs. The disadvantages of embolization procedures are: 1) they often require multiple treatments; and 2) they are not effective in completely obliterating the malformation. Indeed, Gobin et al[10] reported that embolization has little chance of completely occluding an AVM unless the lesion is small or has less than three feeding vessels. However, embolization has been shown to be useful when combined with microsurgery or radiosurgery. Currently, the most widely used embolization technique for AVMs is the injection of acrylic-based glues. Morbidity and mortality rates associated with embolization procedures was reported by Gobin et al[10] as 13% and 2%, respectively.

As discussed above, surgical procedures have advantages and disadvantages in the treatment of AVMs. Recent studies have shown, however, that treating the AVM initially with one or more embolization procedures followed by surgery may provide the best outcome for the patient. When using this approach, the endovascular embolization procedure(s) can reduce

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[4] Schneider BF, Eberhard DA, Steiner LE. Histopathology of arteriovenous malformations after gamma knife radiosurgery. J Neurosurg 1997; 87: 352-357

[5] Szeifert GT, Kemeny AA, Timperley WR, Forster DMC. The potential role of myofibroblasts in the obliteration of arteriovenous malformations after radiosurgery. Neurosurgery 1997; 40: 61-65

[6] The Arteriovenous Malformation Study Group. Arteriovenous malformations of the brain in adults. The New England Journal of Medicine 1999; 340, 23; 1812 – 1818

[7] Schaller C, Schramm J. Microsurgical results for small arteriovenous malformations accessible for radiosurgical or embolization treatment. Neurosurgery 1997; 40: 664 – 674

[8] Lunsford L, Kondziolka D, Bissonette D, Maitz A. Flickinger J. Stereotactic radiosurgery of brain vascular malformations. Neurosurg Clin N Amer 1992; 3: 79 – 98

[9] Kondziolka D, Lunsford L, Flickinger J. Gamma knife stereotactic radiosurgery for cerebral vascular malformations. In: Alexander E, J Loeffler, L Lunsford, ed. Stereotactic Radiosurgery. New York: McGraw-Hill, 1993: 136 – 146

[10] Gobin YP, Laurent A, Merienne L, et al. Treatment of brain arteriovenous malformations by embolization and radiosurgery. J Neurosurg 1996; 85: 19 – 28

the size and vascularity of the AVM prior to microsurgery or radiosurgery and take care of residual malformations following microsurgery or radiosurgery[11]. Vinuela et al[12], reported a cumulative rate of persistent deficits of 9% and a mortality rate of 4% for patients who underwent staged embolization procedures followed by surgical resection. Deruty et al[13], reported in his paper that the contribution of endovascular embolization to the management of cerebral AVMs is generally considered very positive and that it offers great advantages, making surgical resection safer and easier and radiosurgery feasible for large malformations.

The most widely used embolic agents for AVMs are the liquid, acrylic-based glues. Recently, one such glue was approved by FDA (TRUFILL, PMA #P990040, September 25, 2000) for the embolization of cerebral arteriovenous malformations when presurgical devascularization is desired. The challenges faced by clinicians using the acrylic-based glues are the lack of control in delivery of the product and the extreme adhesion to all surfaces, including the catheter.

To provide the physician with an effective liquid embolic agent that may address some of the issues inherent with acrylic-based glues, Micro Therapeutics Inc., has developed the Onyx® Liquid Embolic System (LES™). Onyx LES is intended for use in treating patients with brain AVMs that are intended to undergo subsequent surgical resection. The system is to be used to reduce the vascular supply to the AVM in order to reduce the potential for bleeding during the subsequent surgical resection.

Onyx is a non-adhesive liquid embolic agent comprised of an EVOH (ethylene vinyl alcohol) copolymer dissolved in DMSO (dimethyl sulfoxide), and suspended micronized tantalum powder to provide contrast for visualization under fluoroscopy. The Onyx Liquid Embolic System consists of a 1.5 ml vial of Onyx, a 1.5 ml vial of DMSO, and three 1 ml Onyx delivery syringes. A DMSO compatible delivery micro catheter that is indicated for use in the neurovasculature (e.g. Rebar™ or UltraFlow™ HPC catheters) is used to access the embolization site.

Onyx is delivered through a micro catheter into the feeding vessels of the AVM under fluoroscopic control. The DMSO solvent dissipates into the blood and interstitial fluids, causing the EVOH copolymer and suspended tantalum to precipitate *in situ* into a spongy, coherent embolus. Onyx immediately forms a skin as the polymeric embolus solidifies from the outside to the inside. Since Onyx is non-adhesive, the micro catheter can be left in place while slow, controlled injections are performed. Post embolization angiography can be conducted with the delivery micro catheter in place, enabling the physician to make additional injections of the embolic agent through the same micro catheter, if necessary.

[11] Lawton MT, Hamilton MG, Spetzler RF. Multimodiality treatment of deep arteriovenous malformations: thalamus, basal ganglia, and brain stem. Neurosurgery 1995; 37: 29-36

[12] Vinuela F, Dion JE, Duckwiler G, et al. Combined endovascular embolization and surgery in the management of cerebral arteriovenous malformations: experience with 101 cases. J Neurosurg 1991; 75: 856 – 864

[13] Deruty R, Peilissou-Guyotat I, Morel C, Bascoulergue Y, Turjamn F. Reflectionis on the management of cerebral arteriovenous malformations. Surg Neurol 1998; 50: 245 – 256

Onyx Nomenclature

Three designations have been used for Onyx: one is a historical name, one is a reference to the polymer concentration, and one is currently the product name, which correlates to solution viscosity. Prior to selecting the name Onyx, the historical product name was Embolyx.

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Additionally, MTI has licensed the Onyx LES technology to Genyx Medical, Inc. under the trade name "Uryx" for treatment of female urinary incontinence, and Enteric Medical, Inc. under the trade name "Enteryx" for treatment of gastro-esophageal reflux disease. MTI, Genyx and Enteric have participated in joint biocompatibility and safety studies for the Onyx material. Hence some studies described herein may reference one or more of the trade names Onyx, Uryx or Enteryx.

Current Product Name	Synonymous Name #1	Synonymous Name #2
Onyx-18	Embolyx-6% or Onyx-6%	Embolyx E-6%
Onyx-34	Embolyx- 8% or Onyx-8%	Embolyx E-8%
Uryx	Embolyx - 8% or Onyx-8%	NA
Enteryx	Embolyx - 8% or Onyx-8%	NA

It is important to note that a direct relationship exists between the EVOH concentration and the viscosity. For example, a 6% Onyx solution has an approximate viscosity of 18 cSt and an 8% Onyx solution has an approximate viscosity of 34 cSt. Both solutions – Onyx-18 and -34 – were used for the treatment of AVM in the clinical trial (e.g. ~85% cases were Onyx-18 & ~15% cases were Onyx-34). Given that the majority of test reports refer to the % polymer, this designation will be used throughout this pre-clinical section.

6. SUMMARY OF SAFETY AND EFFECTIVENESS DATA

6.1. Device Generic Name

Artificial Embolization Device (21 CFR 882.5950)

Medical Specialty: Neurology, Product Code HCG, Class III

6.2. Device Trade Name

Onyx® Liquid Embolic System (Onyx® LES):

c) Onyx® 18 (6% EVOH, Model 105-7100-060)
d) Onyx® 34 (8% EVOH, Model 105-7100-080)

6.3. Applicants Name and Address

Micro Therapeutics, Inc.
2 Goodyear
Irvine, CA 92618
Establishment Registration No. 2029214

6.4. Pre-Market Approval Application

TBD

6.5. Date of Panel Recommendation

TBD

6.6. Date of GMP Inspection

May 27, 2003

6.7. Date of Notice of Application Approval

TBD

6.8. Indications for Use

The Onyx® LES is an artificial embolization device intended for use in the treatment of brain arteriovenous malformations, when embolization is indicated to minimize blood loss or to reduce the BAVM size prior to surgery or radiosurgery.

6.9. Device Description

Onyx is the trade name for a liquid embolization device manufactured by Micro Therapeutics, Inc. The device is intended for use by the Interventional Neuro-Radiologist when therapeutic or palliative embolization of a brain arteriovenous malformation (BAVM) is indicated to minimize blood loss or to reduce the BAVM size prior to surgery or radiosurgery.

The liquid Onyx is a simple mixture of ethylene vinyl alcohol co-polymer (EVOH) dissolved in dimethyl sulfoxide (DMSO). Micronized tantalum powder is suspended in the liquid polymer/DMSO mixture to provide fluoroscopic visualization. The Onyx material is delivered in a liquid phase through a micro catheter to the target lesion under fluoroscopic control. Upon contact with blood (or body fluids) the solvent (DMSO) rapidly diffuses away causing in-situ precipitation of a soft radiopaque polymeric embolus.

Onyx is available to the physician in a range of liquid viscosities intended to have delivery and precipitation characteristics optimized for the type of lesion being treated. Lower viscosity Onyx formulations, achieved by reducing the polymer/DSMO ratio, are appropriate for embolization of arteriovenous malformations where depth of penetration in small diameter vessels is required for effective embolization. These Onyx formulations, designated as Onyx-18 and Onyx-34, have a nominal liquid viscosity of 18 and 34 centistokes respectively.

6.10. Principle of Operation

Onyx is a pre-mixed, radiopaque injectable embolic agent that is not a glue and has no adhesive properties. It solidifies through the process of precipitation. Precipitation is initiated when Onyx comes into contact with an aqueous solution (e.g., blood, body fluids normal saline, water) and the solvent DMSO rapidly diffuses out of the polymer mass.

The liquid Onyx is delivered through a DMSO primed micro catheter selectively placed within a feeding pedicle of an AVM. Precipitation or solidification of the material begins immediately upon injection, beginning as a “skin” on the outside of the mass. Total precipitation occurs within minutes. The distance that Onyx travels before solidifying within the vasculature depends on a number of factors, including the flow rate in the vessel and the rate of injection. In AVM applications, embolization is intended to reduce the risk of rupture and subsequent stroke.

6.11. Materials of Composition

6.11.1. Ethylene Vinyl Alcohol Copolymer (EVOH)

Ethylene Vinyl Alcohol Copolymer (EVOH) is the primary component of the Onyx material. The EVOH polymer is synthesized by polymerizing a mixture of ethylene gas (MW 28.05, BP -103.7° C) and vinyl acetate (MW 86.1, BP 72.2° C). The resulting ethyl vinyl acetate is treated in a basic pH environment with sodium hydroxide and methanol to hydrolyze the acetate from the polymeric chain resulting in ethyl vinyl alcohol (EVOH). The EVOH polymer is washed with methanol to remove the acetate and other low molecular weight oligomers.

6.11.2. Dimethyl Sulfoxide (DMSO)

Dimethyl Sulfoxide (DMSO) is used in the Onyx system as a solvent for the EVOH co-polymer. DMSO is a widely used commercial solvent derived from trees as a byproduct from the production of paper. In the body, DMSO rapidly oxidizes to dimethyl sulfone (methlysulfonylmethane-MSM) and dimethyl sulfide. Both DMSO and MSM are quite soluble in both oil and water based liquids. However, dimethyl sulfide is hydrophobic and tends to be insoluble in water and soluble in oil-based liquids. The elimination of DMSO and MSM happens not only by excretion in the urine and feces but also by elimination through the lungs and skin in the form of dimethyl sulfide.

6.11.3. Tantalum

Tantalum: The tantalum component of Onyx is a high radiodensity material that provides fluoroscopic visualization of Onyx when using conventional fluoroscopic equipment. The micronized tantalum has particle size ranging from 0.7 to 22 µm. with approximately 10% of particles greater than 11 µm, 22% between 6 to 11 µm, and 68% less than 5.5 µm. The 33% w/v of tantalum powder in formulation yields excellent visualization of Onyx during embolization procedures. As Onyx precipitates in-situ, the tantalum particles are trapped and encapsulated within the EVOH polymer.

6.12. Onyx LES Kit Components

Onyx is provided in a kit containing one vial of Onyx (1.5 ml), one vial of DMSO (1.5 ml) for priming the micro catheter used during the embolization procedure, and three DMSO compatible syringes (1 ml). Components are provided sterile and non-pyrogenic, for single use only.

6.13. Ancillary Devices

The Onyx material requires use of compatible delivery devices to assure patient safety and effective performance of the embolic material. The Onyx Instructions for Use provides detailed instructions for preparation and use of recommended syringes and

delivery catheters. Each of the recommended devices has been extensively tested for compatibility with the Onyx material, DMSO solvent, and embolization procedures.

6.13.1. MTI UltraFlow? Micro Catheter

The MTI Flow Directed micro catheters are intravascular flow directed micro catheters intended for delivery of physician specified agents for diagnosing or treating vascular diseases of the distal neuro and peripheral anatomy. The catheters are DMSO compatible single lumen end-hole catheters.

6.13.2. MTI Rebar? Micro Catheter

The Rebar catheters are designed for use in the neuro vasculature and for delivery of DMSO and the Onyx liquid embolic material after selective placement in the target lesion. The Rebar catheter is a single-lumen catheter designed to be introduced over a steerable guidewire.

6.13.3. Syringe, 1 ml (DMSO / Onyx Syringes)

Within each Onyx AVM System kit, MTI provides a set of three sterile 1 ml syringes. The syringes are manufactured by MTI using materials compatible with DMSO and Onyx. One syringe is intended for the injection of DMSO, and the remaining two syringes are intended for injection of Onyx. The two syringe types are identical except for the colorant in the plunger and the printing on the outside syringe barrel.

6.14. Cautions, Contraindications, Warnings, and Precautions

6.14.1. Cautions

?? Performing embolization to occlude blood vessels is a high risk procedure. This device should be used only by physicians with neurointerventional training and a thorough knowledge of the pathology to be treated, angiographic techniques, and super-selective embolization.

?? Failure to wait a few seconds to retrieve the micro catheter after Onyx injection may result in fragmentation of Onyx into non-target vessels.

?? Difficult catheter removal or catheter entrapment may be caused by any of the following:

- Angioarchitecture: very distal AVM fed by afferent, lengthened, and tortuous pedicles
- Vasospasm
- Reflux

?? Should catheter removal become difficult, the following will assist in catheter retrieval:

- o Carefully pull the catheter to assess any resistance to removal.
- o If resistance is felt, remove any "slack" in the catheter.
- o Gently apply traction to the catheter (approximately 3-4 cm of stretch to the catheter).
- o Hold this traction for a few seconds and release. Assess traction on vasculature to minimize risk of hemorrhage.
- o This process can be repeated intermittently until catheter is retrieved.

?? For entrapped catheters:

- o Under some difficult clinical situations, rather than risk rupturing the malformation and consequent hemorrhagic complications by applying too much traction on an entrapped catheter, it may be safer to leave the micro catheter in the vascular system.
- o This is accomplished by stretching the catheter and cutting the shaft near the entry point of vascular access allowing the catheter to remain in the artery.
- o If the catheter breaks during removal, distal migration or coiling of the catheter may occur. Same day surgical resection should be considered to minimize the risk of thrombosis.

6.14.2. Contraindications

?? Not for use with premature infants (<1,500 g) or individuals with significant liver function impairment.

6.14.3. Warnings

?? Inspect product packaging prior to use. Do not use if sterile barrier is open or damaged.

?? Verify that adequate sedation is used throughout the embolization procedure. Insufficient sedation may result in patient discomfort or movement. Patient movement during embolic agent injection may result in embolization of an unintended vessel.

NOTE: Adjunctive coil use should be considered if angiography shows that venous drainage of the AVM appears almost simultaneously with arterial opacification. Based on results from *in vitro* and *in vivo* testing, coil placement prior to Onyx injection should be considered for feeding pedicles with AV fistulae having flow rates exceeding 200 ml/min and vessel diameters of 3 mm or greater.

?? Failure to continuously mix Onyx for the required time may result in inadequate suspension of the tantalum, resulting in inadequate fluoroscopic visualization during delivery.

?? Use only MTI micro catheters. Other micro catheters may not be compatible with DMSO and their use can result in thromboembolic events due to catheter degradation.

?? Use only the MTI 1 ml syringe to inject DMSO and Onyx. Other syringes may not be compatible with DMSO.

?? Premature solidification of Onyx may occur if micro catheter luer contacts saline, blood or contrast of any amount.

?? Inject Onyx immediately after mixing. If Onyx injection is delayed, tantalum settling can occur within the syringe resulting in poor visualization of Onyx during injection.

?? Do not exceed 0.3 ml/min injection rate. Animal studies have shown that rapid injection of DMSO into the vasculature may lead to vasospasm and/or angionecrosis.

?? Only use thumb pressure to inject Onyx. Using palm of hand to advance plunger may result in catheter rupture due to overpressurization in the event of catheter occlusion.

?? Adequate fluoroscopic visualization must be maintained during Onyx delivery or non-target vessel embolization may result. If visualization is lost at any time during the embolization procedure, HALT Onyx delivery until adequate visualization is re-established.

?? Do not allow more than 1 cm of Onyx to reflux back over catheter tip. Excessive Onyx reflux may result in difficult catheter removal.

?? After using a micro catheter with Onyx, do not attempt to clear or inject any material through it. Such attempts may lead to embolus or embolization of an unintended area.

?? STOP injection if Onyx is not visualized exiting catheter tip. If the catheter becomes occluded, over-pressurization can occur. During Onyx injection, continuously verify that Onyx is exiting the catheter tip. Testing has shown that over-pressurization and rupture can occur if 0.05 ml of Onyx is injected and is not visualized exiting the catheter tip.

?? STOP injection if increased resistance to Onyx injection is observed. If increased resistance occurs, determine the cause (e.g., Onyx occlusion in catheter lumen) and replace the catheter. Do not attempt to clear or overcome resistance by applying increased injection pressure, as use of excessive pressure may result in catheter rupture and embolization of unintended areas.

?? DO NOT interrupt Onyx injection for longer than two minutes prior to re-injection. Solidification of Onyx may occur at the catheter tip resulting in catheter occlusion, and use of excessive pressure to clear the catheter may result in catheter rupture.

6.15. Potential Adverse Effects of the Device on Health

Safety was examined for all patients enrolled in the clinical trial. This section presents a summary of all patients in the Intention to Treat (ITT) cohort, which includes all patients in which treatment of the assigned device was attempted. Safety was assessed based on the nature and severity of adverse events.

The safety profile for the two groups was also comparable. Although more patients in the Onyx group experienced a serious adverse event, the number of serious adverse events experienced was equal in the two groups, and there was not a statistically significant difference between the two groups for patient based serious AE rates. In addition, many of the events occurred during or post surgery as opposed to during or post embolization with the Onyx Liquid Embolic System. None of the events was considered unanticipated and the rate of the device related adverse events was very similar in both groups.

The table below provides a summary of the hierarchical events with only one event (worst event) listed per patient. A total of 15 patients in the n-BCA group and 19 patients in the Onyx group experienced at least one serious adverse event. The worst event for each patient whether it was the primary or a cascaded event from another less severe event is presented in the table. There were no unanticipated adverse device effects. In the case of the patients that had an event and subsequently expired, the event that is listed in the table is death.

Two patients died during the course of the clinical trial. Both deaths occurred in the Onyx group and both occurred following surgical resection.

There were no unanticipated adverse device events reported in this trial.

	Group	
EVENT NAME	**n-BCA (n=54 pts)**	**Onyx (n=46 pts)**
Death	0 (0%)	2 (4.4%)
Intracranial Hemorrhage	8 (15%)	6 (13%)
Stroke	0 (0%)	1 (2%)
Worsening Neuro Status	5 (9.3%)	7 (15%)
Hydrocephalus	0 (0%)	2 (4.4%)
Seizures	0 (0%)	1 (2%)
Headache +/- nausea and vomiting	2 (3.7%)	0 (0%)
TOTAL	***15***	***19***

Additional adverse events, which may be associated with embolization procedures (including those not observed during the clinical study*) include:

- Access site bleeding
- Headache
- Nausea and vomiting
- Medication reaction
- Patient discomfort
- Cardiac arrhythmia
- Allergic reaction
- Passage of embolic material into normal vessels adjacent to the lesion
- Laboratory/imaging abnormalities
- Infection
- Fever
- Tongue swelling
- Psychotic episode
- Thrombocytopenia
- AVM rupture*
- Pulmonary embolism*

6.16. Alternative Practices And Procedures

Endovascular embolization of cerebral arteriovenous malformations (AVMs) as described in the literature, involves the use of catheters to deliver a variety of occlusive agents such as permanent balloons, sclerosing drugs, thrombosing coils, polyvinyl alcohol (PVA) particles, and rapidly acting glues, such as n-Butyl cyanoacrylate. Currently, the most widely used embolization technique for AVMs is the injection of acrylic-based glues.

6.17. Marketing History

The Onyx LES system was first placed on the market in August 1999, in Europe with the CE mark for use in the treatment of arteriovenous malformations. Onyx continues to be marketed throughout most European countries, Canada, Turkey, Australia, and some Latin American countries. Onyx has not been withdrawn from the market in any country for any reason.

6.18. Summary of Pre-Clinical Studies

This section presents summaries of important preclinical studies in support of safety and effectiveness of the Onyx LES system. The following pre-clinical studies were conducted to ensure that the Onyx LES is safe and effective for its intended use and environment: Mechanical/Chemical Tests, Biocompatibility Studies, Animal Studies, and Pre-trial Clinical Experience.

6.18.1. Mechanical/Chemical Tests

These tests cover the basic characterization of Onyx as a solution and as an implanted precipitate, as well as compatibility with syringes/catheters and other embolic devices, such as coils.

Study	Results and Conclusions
Tantalum Suspension	This test was performed to determine the minimum required shake time to mix and assure homogenous tantalum dispersion in Onyx. Data from this study demonstrates that using the IFU- recommended shake time results in consistent and homogeneous tantalum dispersion within the vial, supported by an appropriate safety factor.
Onyx Solidification Time	To determine Onyx solidification time, MTI precipitated Onyx in saline to create spherical Onyx masses (approximately 3 mm in diameter). At controlled time intervals, MTI compressed the Onyx spheres to determine when liquid could no longer be expelled from the mass. The results demonstrated that Onyx spheres were completely solidified (no liquid expelled from the Onyx mass) within 3 minutes.
Material Expansion	To determine Onyx expansion characteristics during or after precipitation, MTI precipitated several aliquots of Onyx in saline and evaluated the resulting Onyx masses over time for various mechanical properties, including appearance and size. Results demonstrated that the Onyx masses remained coherent for the 7-day test period, with no measurable size differences.
Particulate Generation	To determine whether Onyx generates particles in its final precipitated form, MTI precipitated Onyx in bottles containing 60 mL of saline to create spherical Onyx masses (approximately 3 to 4 mm in diameter). The bottles were capped and repeatedly inverted in order to create fluid shear forces. The Onyx spheres were removed and the effluent tested using a spectrophotometer. The test results demonstrated that Onyx particulate generation was less than the maximum allowable per USP XXV <788> .
Material Adhesion	To characterize the adhesive properties of Onyx, MTI (1) measured the force required to extract various catheters from a precipitated Onyx mass and (2) compared catheter Onyx extraction force to n-butyl cyanoacrylate (n-BCA) embolic agents or "glues." MTI allowed a catheter to remain entrapped in an Onyx mass for 60 minutes. After 60 minutes, when pulled at approximately 1-2 cm, the catheters released from the Onyx mass with relatively low force as compared to the minimum tensile strength requirements of the catheters. No evidence of Onyx adhesion or fragmentation was observed. MTI then allowed a catheter to become entrapped in glue for 2 minutes (due to the adhesive nature of glues, the previous 60-minute wait time associated with Onyx was reduced to 2 minutes). The study demonstrated that glues require significantly higher extraction force (after significantly less time) than Onyx.
Effects of Radiation and Stability Onyx Precipitates	To determine if Onyx precipitates are affected by a radiation dosage of 30 Gray, MTI divided 70 grams of Onyx into small aliquots of precipitate. The test samples were exposed to 30 Gray of radiation at the UCLA Medical Center; aged at 55°C for 210 days (2 year equivalent) and tested for biocompatibility, chemical stability, and physical integrity. The test samples exhibited no significant differences from the control samples. The test results demonstrated that Onyx was unaffected by radiation levels encountered during radiosurgery.
Infusion Pressures	To verify that infusion pressures generated during delivery of Onyx were within safe burst specification limits of the IFU recommended catheters, MTI infused Onyx at various infusion rates at 37°C into the UltraFlow and the Rebar micro catheters. The maximum recommended infusion rate for Onyx is 0.3 ml/min. Onyx at an infusion rate of 0.5 ml/min was considered a worst-case test. The study demonstrated that infusion rates of 0.1 to 0.5 ml/min generated infusion pressures significantly below the minimum burst specification of the IFU-recommended catheters.

Study	Results and Conclusions
Device (Catheter and Syringe) Chemical Compatibility Testing	To determine if DMSO (the active solvent in Onyx) degrades the supplied/recommended delivery devices (the UltraFlow and the Rebar micro catheters and the 1 mL syringes), MTI assessed chemical and functional performance of the delivery devices after exposure to DMSO. MTI infused DMSO through each delivery device, then tested the DMSO-exposed catheters for static burst and tensile strength and the syringes for peak force and visualization of gradations. The test results demonstrated that delivery device strength values (burst, tensile and peak force) and the visibility of the gradations did not degrade after extended DMSO exposure and were significantly similar to non-DMSO exposed samples. MTI also tested the effluent (from the DMSO infusion) through High Performance Liquid Chromatography (HPLC) and compared the result to a pure DMSO control sample. The results showed no additional peaks other than DMSO, demonstrating that DMSO (and therefore Onyx) is chemically compatible with both recommended delivery catheters and the syringes.
Adjunctive Device Compatibility (Coils and Glues)	To verify chemical and functional compatibility of Onyx and DMSO with other embolic devices, MTI identified and tested the following two types of embolic agents: (1) hydraulically delivered 0.010" embolic metal coils; and (2) n-BCA based embolic agents or "glues". The results demonstrated that Onyx successfully solidified and occluded simulated vessels up to 5 mm with deployed coils and that DMSO did not leach any materials from the tested coils. Also, there was no chemical interaction shown with Onyx and histoacryl glue.
Sterilization Validation	Dry Heat sterilization of Onyx and DMSO is performed and validated using a half cycle approach with BI indicators (consistent with EN550) to achieve an SAL of 10^{-6}. Ethylene Oxide Sterilization of the packaged Syringes is performed and validated according to ANSI/AAMI/ISO 11135-1994, Medical Devices Validation and Routine Control of Ethylene Oxide Sterilization.
Package Integrity	The Onyx system was subjected to a Federal Express vibration and drop testing for packages 0 – 75 lbs according to ISTA 1A / D4169 following 4 days at –20ºC, 29 days at 55ºC and humidity less than 20% and 27 days at 55ºC and 70-80% relative humidity. The test results demonstrated appropriate package integrity.
Sterile Product – DMSO and Onyx sterile barrier	To demonstrate appropriate sterile barrier, aged vials (three years accelerated aging) were subjected to pressure leak testing and were tested for sterility. No leaks were observed, and all tested samples were sterile. Based on test results, the sterile barrier vial package system for DMSO and Onyx is an effective sterile barrier.
Onyx Real Time and Accelerated Aging	MTI evaluated the effects of aging on the performance of Onyx by conducting accelerated and real time aging testing to support a 3-year product shelf life. The tests consisted of Leakage, Product Sterility, Cytotoxicity, Molecular Weight Distribution, Viscosity, Density, Precipitation and Extractables on Precipitation. Based on the testing results, Onyx System met the necessary criteria for a 3-year shelf life.
DMSO Real Time and Accelerated Aging	MTI evaluated the effects of aging on the performance of DMSO by conducting accelerated and real time aging testing to support a 3-year product shelf life. The testing consisted of analysis for impurities, including dimethyl sulfone. There were no trends in the levels or types of impurities. Based on the testing results, DMSO met the necessary criteria for a 3-year shelf life.

6.18.2. Biocompatibility Studies

Biocompatibility studies were performed per ISO 10993-1, Biological evaluation of medical devices for permanent implants, blood contact. Additional biocompatibility testing was performed per FDA's *Guidance on Biocompatibility Requirements for Long Term Neurological Implants.*

Summary Table: ISO 10993-1 Biocompatibility Test Results

Test Description	Title	Results
Cytotoxicity	MEM Elution Test Evaluation	No evidence of cytotoxicity at dilution of 1:4 or greater
Cytotoxicity	MEM Elution Test Evaluation of DMSO	No evidence of cytotoxicity at dilution of 1:4 or greater
Sensitization	Guinea Pig Maximization (Magnussen/Kligman Method) (Saline & cottonseed oil extracts)	Grade I, Weak response; equivalent to negative control
Intracutaneous Reactivity	USP Intracutaneous Reactivity (Saline & cottonseed oil extracts)	Met USP requirements
Acute Systemic Toxicity	USP Systemic Toxicity (Saline & cottonseed oil extracts)	Met USP requirements
Subacute Toxicity	Fourteen Day Subacute Intravenous Dosing Study (Saline extract)	Non-Toxic
Implantation	USP Seven Day Muscle Implant	USP requirements not met due to acute tissue response. Greater irritant than control
Implantation	One Year Intramuscular Implant With and Without Tantalum in Rabbits	Stabilized as minimal to mild inflammatory response
Genotoxicity	Bacterial Reverse Mutation Assay Conducted with Test Article Extracts (Saline and DMSO extracts)	Extracts were negative, passed test.
Genotoxicity	In Vitro Mammalian Cell Gene Mutation Test Conducted with Test Article Extracts (Saline and DMSO extracts)	Extracts were negative, passed test.
Genotoxicity	Micronucleus Cytogenic Assay in Mice Conducted with Test Article Extracts (Saline and corn oil extracts)	Extracts were negative, passed test.
Carcinogenicity	Carcinogenicity Using the *ras*H2 Transgenic Mouse Model	Not carcinogenic

6.18.3. Animal Studies

Study of DMSO Angiotoxicity in a Swine Model:

MTI evaluated acute and chronic effects of dimethyl sulfoxide (DMSO) injection into the vascular system by injecting varied DMSO volumes and injection rates into swine rete. MTI used angiography to detect vasospasm or occlusion of the exposed vessels and performed gross and microscopic histological analysis to detect possible angiotoxicity. MTI performed hemodynamic monitoring and clinical evaluation on all test swine. The study indicated that no clinical abnormalities were observed for animals tested with any combination of DMSO volume or injection rate and "slow" DMSO infusion rates (0.33 mL/min) resulted in no evidence for long-term damage to the retia.

Acute and Chronic Histopathological Changes in a Swine AVM Model:

MTI used Onyx 6% to embolize an animal (swine rete) model to establish the effectiveness of Onyx as an occlusive agent, the tolerance of tissues and inflammatory reactions and the likely embolization of non-target areas. MTI used angiography to confirm placement of the delivery catheter, advancement of the Onyx material during delivery and subsequent occlusion of the rete. To establish acute and chronic effects, animals were sacrificed acutely and chronically (3, 6, and 12 months following the embolization). The study indicated that acute and chronic specimens showed total or near total occlusion of the target rete with no evidence of endothelial denudation or arterial wall angionecrosis. No arterial wall angionecrosis or extravasation of embolic material was observed in any specimen. There was no evidence of embolization of non-target areas. Points of focal disruption of the elastica were observed without extravasation of Onyx into the perivascular space, however at 12 months specimens exhibited a substantial decrease in chronic inflammation.

Pathology Comparison to GDCs:

To demonstrate equivalent chronic tissue response to a currently approved embolic device, MTI compared histological and pathological results of Guglielmi Detachable Coils (GDCs) to Onyx at 3 and 6-month chronic periods. The study showed that the Onyx had acceptable tissue response comparable to GDC with inflammation diminishing to mild focal collections of lymphocytes and giant cells in 12-month chronic specimens. Healthy neointimal tissue remodeling with variably mature endothelial cell growth was observed in continuity with the parent artery lumen in all Onyx. The study results indicate that histological and pathological response to Onyx is acceptable and at least equivalent to the response to GDCs.

Biocompatibility for Long Term Neurological Implants:

To characterize the chronic effect of Onyx in direct contact with neurological tissue in the subarachnoid space, MTI injected (cisterna magna) 60 rabbits (15 per group) with either Onyx-6%, Onyx-25%, saline control, or autologous blood control. Within each group, 5 animals each were survived for 2, 4, or 90 days prior to DSA angiography, sacrifice, gross pathology, and histopathology. There was no evidence of direct toxicity of Onyx when injected into the subarachnoid space of a rabbit model.

One-Year Intramuscular Implant Evaluation:

To determine the effects of EVOH with and without tantalum when implanted intramuscularly, thirty rabbits each received six intramuscular injections of either EVOH or EVOH-T and two intramuscular implants of the control article, USP Reference Standard High-Density Polyethylene. The study results demonstrated that there is no difference between the effects (either local or systemic) of EVOH materials when implanted intramuscularly for a period of one year. While chronic minimal to mild inflammation occurred at almost all sites implanted with both EVOH material types, there was no evidence of tissue changes beyond the margins of the implant site, and there was no evidence of implant material migration to other sites.

6.18.4. Pre-trial Clinical Experience

Histopathology Study of AVMs Embolized with Onyx:

Seven patients with AVMs were treated using Onyx as an embolic agent. There were no reported ischemic or hemorrhagic complications resulting from untoward migration or abrupt occlusion of an AVM nidus. In order to assess the histopathologic changes seen in the vasculature exposed to Onyx, BAVMs embolized with Onyx were surgically excised from 7 patients. The histopathology results compared favorably to changes described with endovascular embolization with other commonly used embolic materials, such as cyanoacrylates, polyvinyl alcohol particles, ethanol and combination materials. The use of Onyx for embolization of BAVMs does not appear to be definitively associated with any morphologic changes expected to produce adverse clinical sequelae.

MRI/CT Evaluation of AVMs treated with Onyx or n-BCA:

A retrospective, masked review was conducted on Onyx and n-butylcyanoacrylate (n-BCA) patients to determine if any direct neurotoxicity was detected in the brain post-AVM embolization using current imaging methods. A central reader reviewed pre- and post-embolization MRI or CT scans, from 73 patients. Fifty-four AVM patients were treated with Onyx and 19 AVM patients were treated with n-BCA. All MRI and CT studies were evaluated for the presence or absence of gliosis, encephalomalacia, edema, leptomeningeal or parenchymal enhancement and hemorrhage. The study indicated that there is no imaging evidence that these embolic devices are associated with cerebral imaging abnormalities.

6.18.5. Pre-clinical Studies Conclusion

In conclusion, the pre-clinical data presented in this submission demonstrate that:

?? Onyx and its associated devices performed within engineering specifications.

?? Onyx is biocompatible, non-carcinogenic, and non-toxic to neurological tissue. The data showed that Onyx implantation was coincident with a local inflammatory response that resolved over time.

?? Onyx, tested in relevant animal models, safely and effectively embolized blood vessels. Local inflammatory responses, similar to those observed with GDCs, resolved over time. Angiotoxicity was not observed when Onyx was injected slowly into the blood vessels.

Onyx pre-clinical human experience agreed with the above results and illustrated the promise of the technology for AVM treatment.

6.19. Summary Of Clinical Studies

The purpose of the study entitled "U.S. Multicenter, Randomized, Controlled Study [IDE G000296] Comparing the Performance of Onyx® (EVOH) and TRUFILL® (n-BCA) in the Presurgical Embolization of Brain Arteriovenous Malformations (BAVMs)" was to evaluate the safety and effectiveness of Onyx LES compared to TRUFILL for the presurgical treatment of brain AVMs.

The clinical investigation was approved by FDA to enroll up to 106 patients (53 per treatment arm) at up to 20 clinical sites throughout the U.S. All patients who met the inclusion and exclusion criteria at the investigational sites were randomized to either the Onyx or TRUFILL treatment arms. Patients underwent embolization procedure(s) to reduce the size of the AVM prior to surgical resection. Neurological assessments (i.e., NIH scale, Barthel Index, and Glasgow Index) were performed prior to and post embolization and/or surgical resection, when surgery was performed. Patients without total resection were followed for 1 year. Both safety and efficacy analysis were performed to compare the results of the investigational treatment arm (i.e., Onyx) to the approved, control treatment arm (i.e., TRUFILL, n-BCA). These results and analysis are reported in the following sections of this submission. This multicenter trail was conducted at 20 investigational sites, with a total of 108 patients randomized and 106 patients enrolled.

6.19.1. Study Purpose

The purpose of this study was to obtain prospective clinical data on the performance of Onyx and TRUFILL in the presurgical embolization of AVMs. Device safety was assessed by comparing overall and device-related morbidity and mortality. The primary efficacy endpoint was the angiographic reduction in AVM size (volume) achieved. A level of 50% or greater reduction in size was established as a criterion for success. The objective was to demonstrate that Onyx is no worse than TRUFILL in terms of efficacy within a specified clinical tolerance (20%).

6.19.2. Design

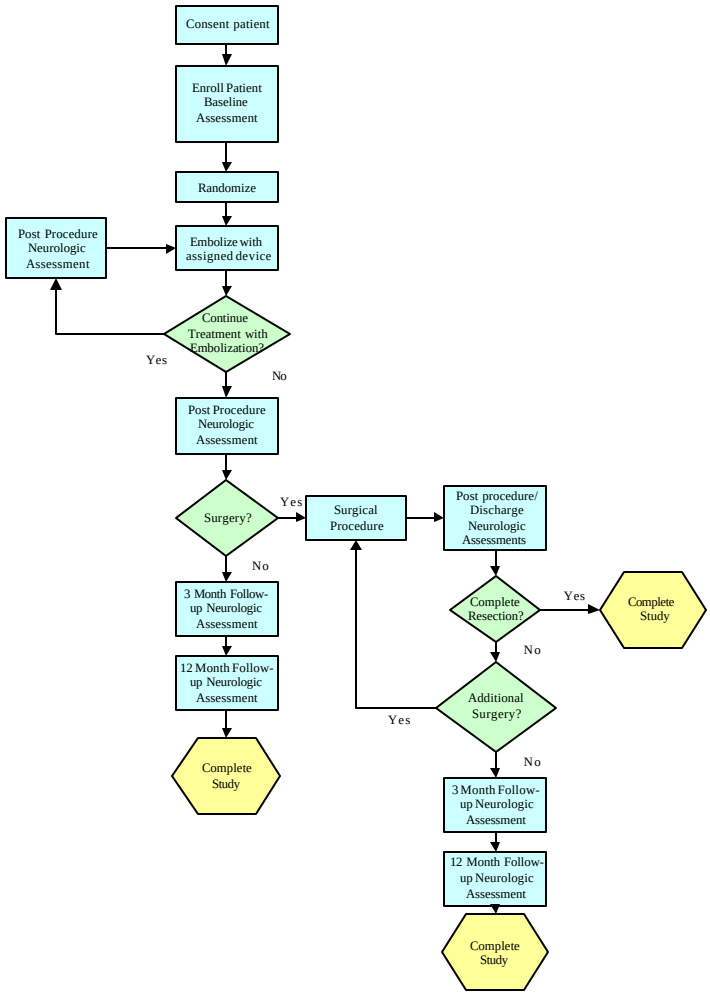
This study was designed as a prospective, randomized, multi-center clinical comparison of the MTI Onyx Liquid Embolic System to the Cordis TRUFILL n-Butyl cyanoacrylate

(n-BCA) liquid adhesive for the presurgical treatment of brain arteriovenous malformations. Patients were randomized on a 1:1 basis for embolization with either Onyx or TRUFILL to result in 53 patients per group.

6.19.3. Methods

Patients were evaluated for potential enrollment based on the inclusion and exclusion criteria of the protocol. Upon enrollment, a baseline clinical neurological examination was performed and grading scales including Barthel Index, Glasgow Coma Scale (GCS) and NIH Stroke Scale (NIHSS) were recorded. In addition, baseline CT, MRI, and/or angiograms were performed for complete characterization of the AVM prior to randomization. Patients were randomized when the AVM and clinical characteristics aligned with the inclusion and exclusion criteria outlined in the clinical protocol. Once randomized, patients entered a regime of embolization as deemed appropriate by the investigator. After each embolization procedure, patients were neurologically evaluated using the same scales as pre procedure except for the Glasgow Scale which was measured utilizing the Glasgow Coma Scale pre procedure and the Glasgow Outcome Scale Post Procedure. Upon completion of the embolization phase, patients were referred for surgery or other nonsurgical course of treatment including radiosurgery or no further treatment. Patients that were completely resected received a final neurological examination with grading scale assessments as a final evaluation of the protocol. Those patients with AVMs that were not completely resected underwent follow-up evaluations at 3 and 12 months. The follow-up assessments included a complete neurological examination with grading scales including Barthel Index, Glasgow Outcome Score (GOS) and NIH Stroke Scale (NIHSS) and evaluation of safety. A clinical protocol summary flowchart is shown below.

Clinical Protocol Summary



6.19.4. Efficacy Endpoints

The primary efficacy measure was technical success as measured by angiographic reduction in AVM size (volume) of 50% or greater as assessed by core laboratory. Angiographic size reduction is defined as the change from the original AVM size prior to any embolization procedure, to the AVM size after the last embolization procedure.

The results for the primary efficacy endpoint demonstrate that the two products are comparable with regard to AVM exclusion efficacy, and thus, the primary study hypothesis (i.e., Onyx is no worse than n-BCA in terms of AVM obliteration defined as = 50% occlusion as assessed by core angiographic laboratory) was achieved using both an Intention to Treat and Per Protocol analysis approach. In fact, the intention to treat analysis demonstrated superiority of the Onyx performance over n-BCA ($p = 0.0377$).

6.19.5. Primary Endpoint Summary

Core Lab Angiographic Success	n-BCA (n= 54)	Onyx (n= 46)	Difference [95% CI]	Relative Risk [95% CI]
Intent-to-Treat Analysis	84.3% (43/51)	97.6% (41/42)	13.3% [2.3%, 24.3%,]	1.16 [1.01,1.32]
Per Protocol Analysis	85.7% (42/49)	95.4% (41/43)	9.6% [-2.0%, 21.3%]	1.11 [0.97, 1.27]

Diff = Onyx – n-BCA; SE = sqrt($p_1q_1/n_1+p_2q_2/n_2$); CI = Diff?1.96*SE
RR = Onyx/n-BCA; SE = sqrt{$(1- p_1)/ n_{11}+(1- p_2)/ n_{21}$}; CI = RR*exp(?1.96*SE)

The study had two secondary efficacy endpoints, surgical blood loss and surgical resection time. There was considerable variability in these endpoints primarily due to the complexity of this disease state and the associated surgery for resection. No statistically significant differences were observed for either of these two secondary endpoints.

6.19.6. Secondary Efficacy Endpoint Summary

Secondary Endpoints	n-BCA (n= 54)	Onyx (n= 46)
Blood loss index ***(p Value = 0.55)***		
mean±sd (n)	892 ± 1067 (44)	1127 ± 1401 (43)
Median	475	550
range (min, max)	100-5000	50-6550
Surgical resection time ***(p Value = 0.99)***		
mean±sd (n)	411 ± 201 (42)	399 ± 179 (42)
Median	344	366
range (min, max)	150, 1019	82, 940

6.19.7. Safety Endpoints

Safety was assessed by the nature and severity of adverse events. An adverse event is defined by the clinical protocol as a clinical deviation away from a patient's baseline health.

The safety profile for the two groups was also comparable. Although more patients in the Onyx group experienced a serious adverse event, the number of serious adverse events experienced was equal in the two groups, and there was not a statistically significant difference between the two groups for patient based serious AE rates. In addition, many of the events occurred during or post surgery as opposed to during or post embolization with the Onyx Liquid Embolic System. None of the events was considered unanticipated and the rate of the device related adverse events was very similar in both groups.

6.19.8. Safety Endpoint Summary

Safety (Pt based) % of patients (pts. with SAE/total sample)	n-BCA (n= 54)	Onyx (n= 46)	p Value*
Serious Adverse Event	27.8% (15/54)	41.3% (19/46)	0.20
System-related SAE	3.7% (2/54)	8.7% (4/46)	0.41
Treatment-related SAE	5.6% (3/54)	10.9% (5/46)	0.46
Surgery related SAE	20.4% (11/54)	21.7% (10/46)	1.00
Disease related SAE	1.9% (1/54)	4.3% (2/46)	0.60

* Fisher's Exact Test

6.19.9. Technical and Procedural Events

Technical Events were reported for each device and included any malfunction of the embolic device or accessory devices (including the delivery catheter) during the embolization procedure. Procedural Events included any unintended or undesirable result, observation or abnormality noted by the physician during the embolization procedure (such as vasospasm or a minor vessel dissection). These events were specifically related to technical aspects of the product or procedural aspects of the treatment and were *NOT* associated with any adverse events. If there was an adverse event that was associated with the investigational product, it was summarized as an adverse event and categorized as system related.

In addition to safety and efficacy, technical and procedural events were analyzed. The results of these analyses demonstrated that the frequency of these types of events between the two treatment groups was comparable, as shown in the table below.

6.19.10. Technical/Procedural Events Summary

	n-BCA (n= 54)	Onyx (n= 46)
Technical Events (# of events)	11	18
Procedural Events (# of events)	12	3
Total Technical/Procedural Events (# of events)	23	21
Percent of Patients with Technical/Procedural Events (# of events/# of patients)* *p=0.91	31.5% (17/54)	30.4% (14/46)

Thus, Onyx demonstrated equivalent performance to n-BCA in terms of technical and procedural performance.

6.19.11. Clinical Study Conclusions

In conclusion, the clinical study has met its study hypothesis, demonstrating non-inferiority of Onyx in comparison to n-BCA in the ability to occlude an AVM prior

to surgical resection. In fact, the Intention to Treat analysis demonstrates superior performance of Onyx over n-BCA. Secondary efficacy endpoint analysis shows no difference in surgical blood loss and surgical resection time between the two groups. Although not a study endpoint, adjunctive use of coils was found to be lower in the Onyx group. The safety profile has been shown to be similar between the two groups. There were no unanticipated adverse device effects, and there were no technical or performance issues that would preclude generalized use of the Onyx system. The summary of this clinical study supports the marketing approval for the Onyx Liquid Embolic System.

6.20. Conclusions

This study provides reasonable assurance of the safety and effectiveness of the Onyx® Liquid Embolic System (Onyx® LES) for the treatment of brain arteriovenous malformations, when embolization is indicated to minimize blood loss or to reduce the BAVM size prior to surgery or radiosurgery.

6.21. Panel Recommendations

TBD

6.22. CDRH Decision

TBD

6.23. Approval Specifications

TBD

7. DEVICE DESCRIPTION

7.1. Trade Name

Onyx® Liquid Embolization System (LES)

a) Onyx 18, Model 105-7100-060

b) Onyx 34, Model 105-7100-080

7.2. Onyx Description

Onyx is the trade name for a liquid embolization device manufactured by Micro Therapeutics, Inc. The device is intended for use by the Interventional Neuro-Radiologist when therapeutic or palliative embolization of a brain arteriovenous malformation (BAVM) is indicated to minimize blood loss or to reduce the BAVM size prior to surgery or radiosurgery.

The liquid Onyx is a simple mixture of ethylene vinyl alcohol co-polymer (EVOH) dissolved in dimethyl sulfoxide (DMSO). Micronized tantalum powder is suspended in the liquid polymer/DMSO mixture to provide fluoroscopic visualization. The Onyx material is delivered in a liquid phase through a micro catheter to the target lesion under fluoroscopic control. Upon contact with blood (or body fluids) the solvent (DMSO) rapidly diffuses away causing in-situ precipitation of a soft radiopaque polymeric embolus.

Onyx is available to the physician in a range of liquid viscosities intended to have delivery and precipitation characteristics optimized for the type of lesion being treated. Lower viscosity Onyx formulations, achieved by reducing the polymer/DSMO ratio, are appropriate for embolization of arteriovenous malformations where depth of penetration in small diameter vessels is desirable for effective embolization. These Onyx formulations, designated as Onyx-18 and Onyx-34, have a nominal liquid viscosity of 18 and 34 centistokes respectively.

Onyx-18 (6%) Vial

Onyx-34 (8%) Vial

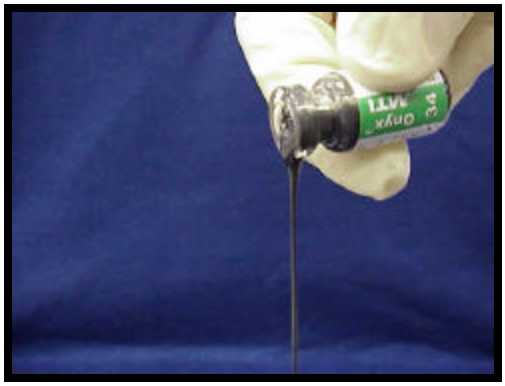
Pure DMSO Vial

The appropriate viscosity for a given procedure is determined by physician preference, the BAVM morphology, and the extent of distal penetration desired. The higher viscosity Onyx 34 (nominal viscosity of 33 cSt at 40 °C) is recommended when feeding pedicle injections will be conducted close to the nidus, at flow rates up to 200 ml/min, and in 3 mm or smaller diameter vessels. The lower viscosity Onyx 18 (nominal viscosity of 18 cSt at 40°C) is recommended when feeding pedicle injections will be conducted close to the nidus, and the flow rate is less than 50 ml/min. Onyx-18 will travel more distally and penetrate deeper into the nidus due to its lower viscosity compared to Onyx-34. Final solidification occurs within five minutes for both product formulations.

7.3. Principle of Operation

Onyx is a pre-mixed, radiopaque injectable embolic agent that is not a glue and has no adhesive properties. It solidifies through the process of precipitation. Precipitation is initiated when Onyx comes into contact with an aqueous solution (e.g., blood, body fluids normal saline, water) and the solvent DMSO rapidly diffuses out of the polymer mass.

The liquid Onyx is delivered through a DMSO primed micro catheter selectively placed within a feeding pedicle of an AVM. The DMSO priming volume assures separation of Onyx from blood, saline or contrast media within the catheter lumen that may cause early precipitation and catheter occlusion. The Onyx material is injected into the AVM at a slow rate of approximately 0.16 ml/min. Precipitation or solidification of the material begins immediately upon injection, beginning as a “skin” on the outside of the mass. Total precipitation occurs within minutes. The distance that Onyx travels before solidifying within the vasculature depends on a number of factors, including the flow rate in the vessel and the rate of injection. In AVM applications, embolization is intended to reduce the risk of rupture and subsequent stroke.



Liquid Onyx-34 (8%)

Onyx Precipitation in Saline

7.4. Onyx Formulation Specification

The following table specifies the formulation and the components of Onyx-18 (6%) and Onyx-34 (8%).

(---------- Data Redacted ----------)

7.5. Onyx Viscosity Validation

The Onyx formulations have been characterized by their kinematic viscosity and are measured in Centistokes (cSt). For example, Onyx-18 (6% EVOH) has an approximate viscosity of 18 cSt and Onyx-34 (8% EVOH) has an approximate viscosity of 34 cSt at 40°C. Validation activities were performed on various attributes of the Onyx formulations including kinematic viscosity. Post sterilization viscosity measurements were taken using calibrated glass Zeitfuchs (capillary) cross-arm viscometers. Test results met all acceptance criteria and yielded average viscosities within the specifications.

(---------- Data Redacted ----------)

7.6. Onyx Precipitate Morphology

The internal and external morphology of a solidified Onyx mass is shown in the pictures below. Onyx formulations, ranging from 6% - 50%, were precipitated in saline forming spheres of approximately 3 mm in diameter. The Onyx spheres were solidified, sectioned, and examined under high magnification. Results showed that as the % EVOH increased, the outside surface of the spheres became smoother in appearance. Internal morphology revealed a soft spongy mass containing several small voids. Voids decreased as % EVOH increased (e.g. higher viscosity Onyx formulations).

(---------- Data Redacted ----------)

7.7. Materials of Composition

7.7.1. Ethylene Vinyl Alcohol Copolymer (EVOH)

Ethylene Vinyl Alcohol Copolymer (EVOH) is the primary component of the Onyx material. The EVOH polymer is synthesized by polymerizing a mixture of ethylene gas (MW 28.05, BP -103.7° C) and vinyl acetate (MW 86.1, BP 72.2° C). The resulting ethyl vinyl acetate is treated in a basic pH environment with sodium hydroxide and methanol to hydrolyze the acetate from the polymeric chain resulting in ethyl vinyl alcohol (EVOH). The EVOH polymer is washed with methanol to remove the acetate and other low molecular weight oligomers.

(---------- Data Redacted ----------)

The homopolymers of EVOH, polyethylene and polyvinyl alcohol (PVA), from which the copolymer EVOH is derived, have a long history as implant materials. Polyethylene is used in numerous implant applications, including surgical spinal cable, auricular reconstruction, prostheses for spinal disk replacement, and in joint implants for the acetabular, patellar, and tibial surfaces. In addition to these well-established uses, polyethylene is a USP reference standard often employed as a negative polymer control during biocompatibility testing. Similarly, PVA has been used clinically in topical ophthalmic solutions, plasma expanders, and, in the application most closely related to Onyx, as a permanent particle embolization material. The ethylene vinyl alcohol copolymer is used as a hemodialysis and plasmapheresis membrane.

7.7.2. Dimethyl Sulfoxide (DMSO)

Dimethyl Sulfoxide (DMSO is used in the Onyx system as a solvent for the EVOH co-polymer. DMSO is a widely used commercial solvent derived from trees as a byproduct from the production of paper. In the body, DMSO rapidly oxidizes to dimethyl sulfone (methlysulfonylmethane-MSM) and dimethyl sulfide. Both DMSO and MSM are quite soluble in both oil and water based liquids. However, dimethyl sulfide is hydrophobic and tends to be insoluble in water and soluble in oil-based liquids. The elimination of DMSO and MSM happens not only by excretion in the urine and feces but also by elimination through the lungs and skin in the form of dimethyl sulfide.

DMSO is a widely used treatment for interstitial cystitis (IC). Its liquid form, *Rimso-50*, was approved by the FDA for use in treating IC in 1978 (NDA 017788). In this application a 50% solution of DMSO is instilled intravesically via catheter into the bladder for10-20 minutes. The solution has both anti-inflammatory and analgesic properties. It is believed to inhibit free-radical production, thus reducing pain and inflammation. It also aids in the absorption of other bladder-instilled medication.

(----------Data Redacted ----------)

7.7.3. Tantalum

Tantalum: The tantalum component of Onyx is a high radiodensity material that provides fluoroscopic visualization of Onyx when using conventional fluoroscopic equipment.[14]

(----------Data Redacted ----------)

In addition to high radiodensity properties, tantalum was chosen as the contrast agent because it is insoluble, inert, and has a history of successful use in medicine.[15] Tantalum powder has been used successfully over many years by several investigators as a radiocontrast agent in embolic compositions such as PVA particles, cyanoacrylate glues and silicones.[16, 17, 18, 19] Tantalum is an inert metal with a history of use in implants requiring incorporation of a contrast agent, such as arterial stents, hip prostheses, and embolization materials. In addition to its use in embolization materials, tantalum powder has been used as a contrast agent injected into the cervical spinal cord for visualization during percutaneous cordotomy. Additionally, tantalum powder has found uses in neurosurgery, to mark the plane of section in lobotomy or leucotomy, to provide visualization or definition of a site for tumor removal, and for detection of recurrent subdural hematoma after surgery.

7.8. Component Material Source

(---------- Data Redacted ----------)

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7.9. Onyx LES Kit Components

Onyx is provided in a kit containing one vial of Onyx (1.5 ml), one vial of DMSO (1.5 ml) for priming the micro catheter used during the embolization procedure, and three DMSO compatible syringes (1 ml). Components are provided sterile and non-pyrogenic, for single use only.

Onyx and DMSO are packaged in 2mL glass injection vials each with an elastomeric stopper crimped in place with an aluminum cap. The cap does not contact the Onyx or DMSO solution at any time.

The glass vial is low extractable highly resistant borosilicate glass that meets ASTM Type I, Class A and USP Type I standards. This is a glass type defined in the USP as suitable for pharmacopeial preparations and is typically used for heat sterilized, parentrally administered solutions. The vial stopper is an elastomeric chlorobutyl-isoprene blend with a Teflon™ (tetrafluroethylene) liner for all surfaces in contact with Onyx or DMSO.

7.10. Ancillary Devices

The Onyx material requires use of compatible delivery devices to assure patient safety and effective performance of the embolic material. The Onyx Instructions for Use provides detailed instructions for preparation and use of recommended syringes and delivery catheters. Each of the recommended devices has been extensively tested for compatibility with the Onyx material, DMSO solvent, and embolization procedures. Relevant compatibility data is provided in the Pre-clinical Studies section of this submission.

The ancillary devices referenced below have been approved for CE marking in accordance with the requirements of ISO 9001 Quality System, EN 46001, Medical Device Particular Requirements for the Application of EN ISO 9001; and FDA cleared for commercial distribution in the U.S. as noted.

7.10.1. MTI UltraFlow? Micro Catheter

The MTI Flow Directed micro catheters are intravascular flow directed micro catheters intended for delivery of physician specified agents for diagnosing or treating vascular diseases of the distal neuro and peripheral anatomy. The catheters are generally inserted via a femoral artery puncture site and advance to the desired vascular anatomy.

The catheters are DMSO compatible single lumen end-hole catheters. The catheters have a semi-rigid proximal shaft that tapers into a highly flexible distal end section to facilitate

catheter advancement in the distal peripheral and neuro vasculature. The proximal end of the catheter incorporates a standard luer adapter hub to facilitate attachment of accessories. The distal end of the catheter has a radiopaque marker band for fluoroscopic visualization.

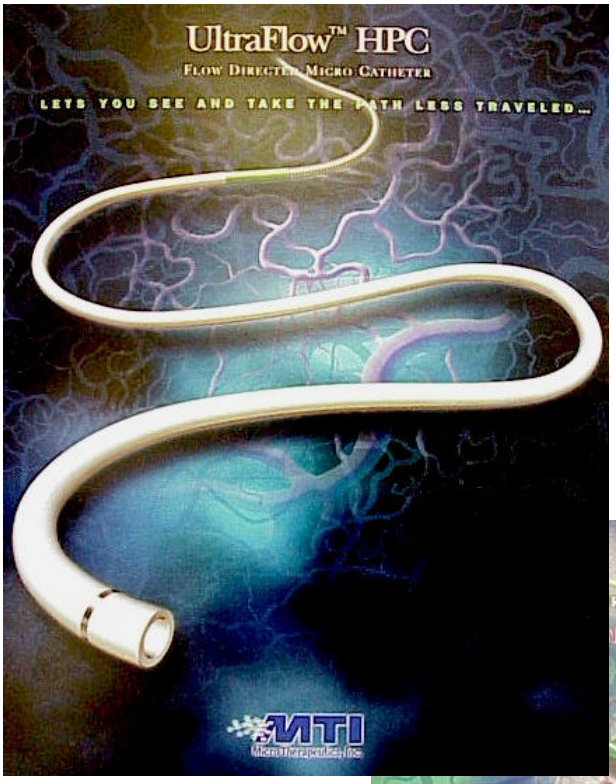
Initially introduced in 1998 as the FlowRider Flow Directed Catheter (Model 105-5060), the catheter has undergone performance improvements and is currently marketed as the UltraFlow HPC Flow Directed Micro Catheter, Models 105-5065 and 105-5066. (Note: Previous catheter names "EnRoute" and “Modified FlowRider” were abandoned due to trademark conflicts.) Re.: 510(k) - K980104, K010004, K024118

7.10.2. MTI Rebar? Micro Catheter

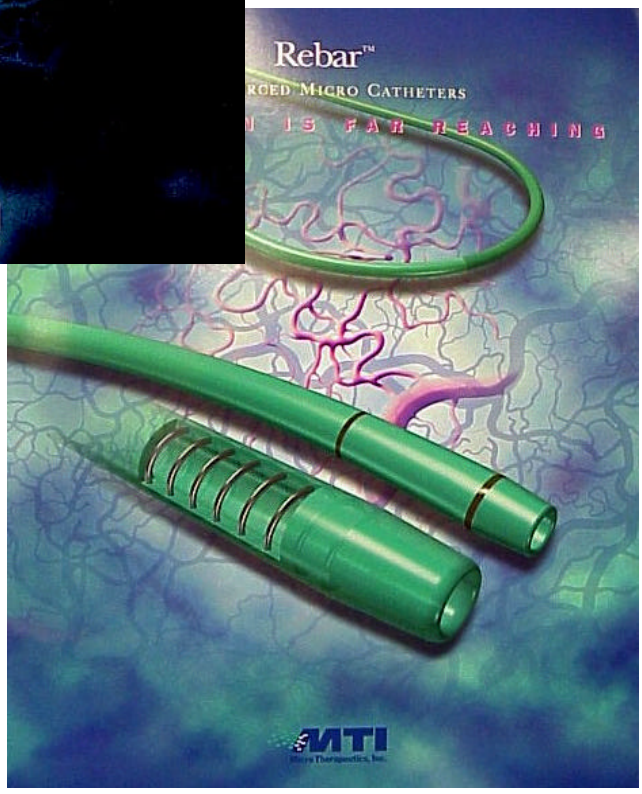
The Rebar catheters are designed for use in the neuro vasculature and for delivery of DMSO and the Onyx liquid embolic material after selective placement in the target aneurysm. The Rebar catheter is a single-lumen catheter designed to be introduced over a steerable guidewire. The catheter has a semi-rigid proximal shaft which transitions into the flexible distal shaft to facilitate catheter advancement in the neuro vasculature. The catheters have dual radiopaque markers at the distal end to facilitate fluoroscopic visualization. The catheters have a hydrophilic outer surface coating. Re.: 510(k) - K993672, K001966

7.10.3. Syringe, 1 ml (DMSO / Onyx Syringes)

Within each Onyx AVM System kit, MTI provides a set of three sterile 1 ml syringes. The syringes are manufactured by MTI using materials compatible with DMSO and Onyx. One syringe is intended for the injection of DMSO, and the remaining two syringes are intended for injection of Onyx. The two syringe types are identical except for the colorant in the plunger and the printing on the outside syringe barrel. The color differences between the two syringes facilitate the delivery of their intended injectants. The three syringes are packaged within a sterile Tyvek peel pouch and chipboard carton. Re.: 510(k) - K991225



DMSO & Onyx Compatible UltraFlow HPC Micro Catheter



DMSO & Onyx Compatible Rebar™ Micro Catheter

8. PRE-CLINICAL STUDIES

8.1. Pre-Clinical Summary

The Mechanical/Chemical Tests present in vitro data collected on Onyx as a precipitate and as a liquid injected through accessory devices. These tests cover the basic characterization of Onyx as a solution and as an implanted precipitate through to its compatibility with syringes/catheters and other embolic devices (e.g. Guglielmi Detachable Coils). The combined conclusion from these tests demonstrates that the mechanical/chemical behavior of Onyx and its accessory devices, from sterile, packaged product to final implant, is well characterized within engineering specifications.

The Biocompatibility Studies present the ISO-10993-1 tests, a neurological implant test, and DMSO safety/toxicology data. The ISO-10993-1 tests used Onyx-8% that contains the greatest amount of polymer in the final implant configuration, which is worst-case. Departures from this strategy were made for two specific tests. The carcinogenicity test in transgenic mice was performed with Onyx-6% at two different dosing volumes to give a high and low range. The neurological implant study in the rabbit cerebellomedullary cistern was performed with Onyx-6% and with Onyx-25% to ensure adequate safety margin. Additional information is presented on the stability and toxicology of DMSO. In total, these reports show that Onyx injections in the cerebrovasculature are safe.

The Animal Studies extend the characterization and safety data by illustrating the safe and efficacious use of Onyx in several animal models. Two peer-reviewed, published swine neurovacular studies show that (1) Onyx is safe and effective for vascular embolization and that (2) the injection of the DMSO/EVOH/Ta solution can be accomplished without angiotoxicity. Although not an AVM study, an aneurysm study was performed in surgically created swine aneurysms with GDC controls that demonstrated comparable tissue responses between Onyx and GDC. These relevant animal models demonstrated that Onyx safely and effectively embolized blood vessels, without angiotoxicity or systemic complications.

The pre-trial Human Experience demonstrates consistent results when compared to the above safety and efficacy data. Seven AVM patients treated with Onyx showed histopathological results that were comparable to other embolic agents such as cyanoacrylate, poly vinyl alcohol, ethanol, and combination materials. Finally, MRI/CT scans from AVM patients treated with Onyx and n-BCA were reviewed and did not show any cerebral imaging abnormalities. The preliminary patient data agree with the above in vitro/in vivo data and suggest the promise of the Onyx AVM treatment.

(---------- Data Redacted ----------)

9. CLINICAL STUDY RESULTS

9.1. Overview of Clinical Trial

The PMA summary data presented were collected under IDE G000296. A summary of the clinical protocol is provided in Exhibit 4. A review of the regulatory history for this IDE is provided in Exhibit 5. Copies of the two clinical protocols with the Case Report Forms (Version C and D) are located in Exhibits 6 and 7, respectively. An IDE supplement was approved for an additional 20 patients (Protocol Rev. E, Exhibit 8). It should be noted that this version of the protocol is currently enrolling patients and at the time of this writing a total of 10 patients have been enrolled. The results for this cohort of patients are not included as part of this summary and will be provided as an update report to the PMA within three months of the PMA filing date. Device accountability for the investigational system has been compiled and is presented in Exhibit 9.

(---------- Data Redacted ----------)

10. OTHER RELEVANT STUDIES AND PUBLICATIONS

The following section contains information available from Micro Therapeutics, Inc. regarding the use of Onyx. This section is separated into three parts; 1) clinical studies conducted using Onyx in brain AVMs; 2) analysis of post-embolization imaging when either Onyx or n-BCA was used as the embolic agent, and; 3) other published literature on the clinical and non-clinical use of Onyx in various anatomic locations.

(---------- Data Redacted ----------)

10.16. Other Published Onyx Reports

The following section presents abstracts and summaries from published animal studies and/or human clinical experience using the Onyx Liquid Embolic System (LES). The discussions generally conclude that polymer/DMSO based liquid embolics are safe and efficacious for treatment of a variety of neurovascular lesions when used in a slow and controlled delivery procedure. Publication of studies, case reports and clinical experience include the following:

- Non-adhesive liquid embolic agent for cerebral arteriovenous malformations: preliminary histopathological studies in swine rete mirabile.
- A reexamination of the angiotoxicity of superselective injection of DMSO in the swine rete embolization model.
- Treatment of Type 11 Endoleaks with Onyx
- Embolization of Arteriovenous Malformations with Onyx: Clinicopathological Experience in 23 Patients
- Embolization of Spinal Cord Arteriovenous Malformations with an Ethylene Vinyl Copolymer Dissolved in Dimethyl Sulfoxide (Onyx Liquid Embolic System).
- Endovascular Treatment of Experimental Aneurysms by Use of a Combination of Liquid Embolic Agents and Protective Devices.
- Head and Neck Hypervascular Lesions: Embolization with Ethylene Vinyl Alcohol Copolymer – Laboratory Evaluation in Swine and Clinical Evaluation in Humans.
- Treatment of Pelvic Arteriovenous Malformations with Ethylene Vinyl Alcohol copolymer (Onyx)
- A New Liquid Embolic Material for Liver Tumors
- Surgical handling characteristics of an ethylene vinyl alcohol copolymer compared with N-butyl cyanoacrylate used for embolization of vessels in an arteriovenous malformation resection model in swine

Abstracts of these studies follows.

10.16.1. Non-adhesive liquid embolic agent for cerebral arteriovenous malformations: preliminary histopathological studies in swine rete mirabile

OBJECTIVE*:* To assess acute and chronic histopathological changes observed in a swine arteriovenous malformation model after endovascular delivery of Embolyx E (Micro Therapeutics Inc., San Clemente, CA) and its organic solvent dimethyl sulfoxide (DMSO). To develop standard endovascular delivery techniques of Embolyx through microcatheters into swine rete mirabile (RMB).

METHODS*:* Forty RMBs in 22 swine were used to analyze acute and chronic angiographic and histological changes after superselective delivery of Embolyx E and/or its organic solvent (DMSO). Four RMBs (two for DMSO and two for Embolyx E study) were used as control specimens. Angiographic and histological evaluations were obtained 18 days, 1 month, 3 months, and 6 months after the procedure. Particular attention was paid to the presence of focal or diffuse angionecrosis, arterial revascularization, and perivascular inflammatory response.

RESULTS: Staged and/or continuous delivery of Embolyx E were performed through the DMSO-compatible microcatheters without untoward catheter "gluing." All subacute/chronic specimens embolized with Embolyx E showed no evidence of angiographic recanalization. Twelve RMBs were used in acute studies, and all specimens showed no evidence of angionecrosis or aggressive inflammatory reaction. Subacute and chronic (total, n = 14) histological examinations of the RMBs showed mild inflammatory response manifested by monocellular infiltration and scattered foreign body giant cell reaction. In the 9 of 14 subacute and chronic specimens, focal disruption of elastica was observed along with embolic materials. Fourteen RMBs in eight swine were used to determine the safety range for DMSO injection. Two RMBs were used as control specimens. Rapid intra-arterial delivery (0.5 ml/5-15 s, n = 6) of DMSO caused angiographic vasospasm and histological endothelial necrosis. Slow injection (0.5 ml/30-120 s, n = 8) of DMSO showed minimum or no angiographic vasospasm, minimal adventitial inflammatory response, and no clinical complications.

CONCLUSION: Embolyx E, an occlusive and non-adhesive embolic agent, is capable of producing permanent occlusion of swine RMB with the development of mild intra- and perivascular inflammatory changes and no clinical complications. The slow endovascular delivery of DMSO produces no untoward angiographic, pathological, or clinical changes. A fast injection of DMSO causes endothelial necrosis and severe inflammatory response in the arterial wall. This embolic material seems to have appropriate biochemical, anatomic, and histopathological characteristics to be used in the treatment of cerebral arteriovenous malformations or vascular cranial base tumors.

Murayama Y, Viñuela F, Ulhoa A, Akiba Y, Duckwiler GR, Gobin YP, Vinters HV, Greff RJ. Non-adhesive liquid embolic agent for cerebral arteriovenous malformations: preliminary histopathological studies in swine rete mirabile. Neurosurgery 43(5):1164-75, 1998

10.16.2. A reexamination of the angiotoxicity of superselective injection of DMSO in the swine rete embolization model

BACKGROUND AND PURPOSE: There are a variety of embolization applications for non-adhesive, liquid agents. We reevaluated the potential microvascular angiotoxicity of superselective infusions of dimethyl sulfoxide (DMSO) using very long infusion rates in a previously described animal model.

METHODS: Twenty-six swine underwent percutaneous femoral puncture for superselective catheterization of the artery of the rete while being continuously monitored for ECG and intraarterial pressure. Two volumes (0.5 or 0.8 mL) and three durations (30, 60, and 90 seconds) of superselective infusion of DMSO were used to evaluate the effect of a single-dose rate within an ipsilateral rete. Contralateral control infusions of normal saline were also administered. Acute hemodynamic and angiographic outcomes were assessed. After recovery, follow-up angiography and sacrifice were performed at either 10 or 28 days. Brains and retia were harvested for gross and microscopic histopathologic evaluation.

RESULTS: No significant hemodynamic alterations occurred acutely. Twenty-three of the 24 infused retia showed variable acute vasospasm that typically was mild to moderate in severity and transient (10 to 20 minutes). Follow-up angiography at sacrifice always showed normal retial arterial anatomy. No adverse clinical sequelae were noted. Gross inspection of brains showed no evidence of infarction or subarachnoid hemorrhage. Microscopic histopathologic examination of retia showed mostly nonspecific changes in both exposed and control samples. Possible causal histotoxicity was seen in four retia (three of four exposed to higher dose rates), in which involvement was limited to one to three retial arteries.

CONCLUSION: Lower total dose and dose rates of superselective infusion of DMSO into the retial microarterial network resulted in substantially less angiotoxicity than that found in a previous study, as defined by clinical, angiographic, gross, and histopathologic criteria.

Chaloupka JC, Huddle DC, Alderman J, Fink S, Hammond R, Vinters HV: A reexamination of the angiotoxicity of superselective injection of DMSO in the swine rete embolization model. AJNR Am J Neuroradiol 20:401-410, 1999

10.16.3. Treatment of Type 11 Endoleaks with Onyx

OBJECTIVE*:* Endoleaks are defined as persistent perfusion of an abdominal aortic aneurysm (AAA) after endovascular stent-graft deployment. The authors describe their experience treating six endoleaks with the liquid embolic agent Onyx (ethylene-vinyl-alcohol copolymer).

BACKGROUND*:* Type 11 endoleaks have been treated surgically, both with graft explantation and, more recently, with retroperitoneal ligation of collateral feeding vessels. These invasive methods require hospital admission and carry with them the accompanying morbidity of surgery. Several reports of treatment of type 11 endoleaks with use of vascular coils have been published, typically describing the selective

catheterization and occlusion of a single feeding vessel. In three of the five type 11 endoleaks in our series, two or more vessels were involved. Occlusion of a single feeding vessel with a coil in these cases may have allowed continued perfusion of the endoleak, and, as a result, continued pressurization of the aneurysm sac. Recanalization of blood flow within the interstices of coils and coil compaction also potentially limit the effectiveness and durability of coil repair of type 11 endoleaks.

METHODS*:* Translumbar access of the endoleaks was attempted in four patients (Fig 1). Patients were positioned prone and intravenous sedation was administered. Prophylactic antibiotics were not given. A suitable direction of endoleak puncture was selected by reviewing CT images. A 3-F DMSO-compatible microcatheter (Rebar-14 or Rebar-27; Micro Therapeutics) was passed coaxially into the endoleak sac. Onyx was slowly injected while the delivery catheter was gradually withdrawn, forming a cast of the endoleak sac. Translumbar sheaths were removed at the termination of the embolization procedure and the patients were positioned in a supine position to apply pressure from their own weight to the puncture site.

RESULTS*:* Complete endoleak occlusion was achieved in five of six cases. Follow-up imaging has demonstrated decreased aneurysm diameter in all patients 7-29 weeks (mean = 19.2 weeks) after treatment. In our experience, embolization of type 11 endoleaks with use of the liquid embolic agent Onyx was feasible and, in early follow-up, successful. Procedure times were short, the majority of patients were treated on an outpatient basis, and no persistent complications were encountered.

CONCLUSION*:* The principal advantage of the use of a liquid embolic agent in the treatment of type 11 endoleaks relates to the ability of a liquid to fill the endoleak sac completely, including all inflow and outflow vessels, without selective catheterization of each patent vessel. The solid cast formed by a liquid embolic agent should result in a noncompressible structure through which recanalization does not occur, providing more durable repair than that provided by coils.

Martin M, Dolmatch B, Fry P, Machan L. Treatment of Type 11 Endoleaks with Onyx. J Vascular and Interventional Radiology Vol. 12 No. 5 May 2001

10.16.4. Embolization of Arteriovenous Malformations with Onyx: Clinicopathological Experience in 23 Patients

OBJECTIVE*:* To report our experience in treatment of arteriovenous malformations (AVMs) using a new liquid embolic agent, Onyx (Micro Therapeutics, Inc., Irvine, CA).

METHODS: Between January 1998 and May 1999, 23 patients (8 men and 15 women) were treated. The patients' average age was 40 years, with seizure being the most common presenting symptom (39%). The average Spetzler-Martin grade on presentation was 3. The average AVM volume before embolization was 14.5 CM3.

RESULTS: We observed an average 63% reduction in AVM volume after 129 arterial feeders were embolized. There were four adverse events. Two patients experienced ischemia because of inadvertent occlusion of an arterial feeder. One of these patients made a full recovery, but the other patient had a permanent deficit. Two other patients

experienced transient neurological deficits that resolved within 1 week of embolization. Permanent morbidity was thus 4% (1 of 23 patients). There were no deaths. Twelve patients underwent subsequent radiosurgery, and 11 patients had surgery that resulted in complete resection of their AVMs. Histopathological examinations showed mild acute inflammation in specimens resected 1 day after embolization. Chronic inflammatory changes were observed in specimens resected more than 4 days after embolization. In two patients, angionecrosis of the embolized vessels was noted. No evidence of parenchymal hemorrhage was observed in these patients, and vessel wall integrity was maintained as well.

CONCLUSION: Onyx is a new non-adhesive liquid embolic agent that has been used to treat 23 patients at our institution with good results. Its non-adhesive nature and ease of use make it a promising agent in the future treatment of AVMs.

Jahan R, Y, Gobin P, Duckwiler G, Vinters H, Vinuela F. Embolization of Arteriovenous Malformations with Onyx: Clinicopathological Experience in 23 Patients. Neurosurgery Vol. 48 No. 5 May 2001

10.16.5. Embolization of Spinal Cord Arteriovenous Malformations with an Ethylene Vinyl Copolymer Dissolved in Dimethyl Sulfoxide (Onyx Liquid Embolic System).

OBJECTIVE: The authors describe the first use of a new liquid embolic agent (Onyx) to treat spinal cord arteriovenous malformations (AVMs).

METHODS AND MATERIALS: Following superselective angiography to delineate the angioarchitecture of the malformation in Patient #1, 0.2 ml of 6% Onyx liquid embolic material was injected through a flow directed microcatheter. The malformation was on the anterior aspect of the spinal cord at the C-5 level. Similarly, for Patient #2, following MRI and angiography a complex malformation was identified at T-11. 0.2 ml of 6% Onyx was injected in the malformation using a flow directed microcatheter. 0.6 ml6% Onyx was also injected proximal to a fistula associated with the malformation. A second procedure was performed 4 weeks later on patient #2 to occlude completely a residual nidal component of the malformation.

RESULTS: The malformation in patient #1 was successfully obliterated following delivery of the Onyx solution. There was no adherence of the Onyx to the catheter. The patient experienced marked motor weakness immediately following the procedure that largely resolved over 48 hours with a mild residual proximal arm weakness and left leg weakness. The cause of the neurological deterioration is unknown. The malformations in patient #2 were successfully treated and showed no blood flow through the fistulous component and diffuse, slow blood flow through the nidal component. There were no neurological complications in patient #2.

CONCLUSION: Because its properties make it more predictable to use than currently available liquid agents, the authors believe that this material has great potential in the endovascular management of both spinal cord and brain AVMs.

Molyneux A, Chir B, Coley S: Embolization of Spinal Cord Arteriovenous Malformations with an Ethylene Vinyl Copolymer Dissolved in Dimethyl Sulfoxide (Onyx Liquid Embolic System). J Neurosurg (Spine 2) 93:304-308, 2000

10.16.6. Endovascular Treatment of Experimental Aneurysms by Use of a Combination of Liquid Embolic Agents and Protective Devices.

BACKGROUND AND OBJECTIVE*:* The use of liquid embolic agents for embolization of cerebral aneurysms has been reported in the neurosurgical literature. The most important limitation of this technique is the relatively poor control of migration of the liquid ernbolic agent into the parent artery. We performed an experimental aneurysm study using a liquid embolic agent and different protective devices to evaluate the safety and technical feasibility of this endovascular technique.

METHODS: Forty lateral aneurysms were surgically constructed on 20 common carotid arteries of swine. Onyx alone was used to obliterate eight aneurysms. Onyx was also used in combination with microcoils (n = 11), microstents (n = 6), balloons inflated proximally to the neck of the aneurysm (n = 6), and across the neck of the aneurysm (n = 7). One control aneurysm was embolized with Guglielmi detachable coils (GDCs) alone.

RESULTS: The use of a microballoon across entire neck of the aneurysm, a microstent deployed across the neck of the aneurysm, or the deposit of GDCs into the aneurysm allowed faster and more complete filling of the aneurysm with Onyx. However, these protection devices did not totally preclude intractable migration of Onyx into the parent artery (migration rate, 9-33%.

CONCLUSION: Although complete occlusion of experimental aneurysms with Onyx is feasible using protective devices, migration of the liquid embolic agent into the parent artery or intracranially remains a difficult challenge. Further experimental studies need to be performed to master this technique and to select those aneurysms that can be safely treated in clinical practice.

Murayama Y, Vinuela F, Takeshima S, Vinuela F Jr., Akiba Y; Endovascular Treatment of Experimental Aneurysms by Use of a Combination of Liquid Embolic Agents and Protective Devices. AJNR Am J Neuroradiol 21:1726 1735. October 2000

10.16.7. Head and Neck Hypervascular Lesions: Embolization with Ethylene Vinyl Alcohol Copolymer – Laboratory Evaluation in Swine and Clinical Evaluation in Humans.

OBJECTIVE*:* (a) To assess in swine long-term (12-month) histopathologic changes, particularly, those related to recanalization and angiotoxicity after endovascular delivery of ethylene vinyl alcohol copolymer (EVAC), and (b) to evaluate initial clinical experience in 18 patients with head and neck tumors and arteriovenous malformations.

MATERIALS AND METHODS: Embolization with EVAC was performed in one rete each in five swine. After 12 months, an angiogram was obtained, and the contralateral

rete was also embolized (acute). Swine were sacrificed and the retia harvested for pathologic examination. In the clinical study, 18 patients with tumors (n = 14), facial arteriovenous malformations (n = 3), and vertebral arteriovenous fistula (n = 1) underwent therapeutic embolization. The technical aspects of EVAC embolization, percentage of occlusion, and clinical complications were evaluated.

RESULTS: Angiographic 12 month follow-up in swine revealed persistent occlusion of the embolized rete or retia. Histologic examination of the same rete showed vascular occlusion and moderate intraluminal foreign body giant cell reaction; the acutely embolized rete showed no endothelial denudation or angionecrosis. Clinical evaluation in patients revealed satisfactory penetration of lesion vasculature with EVAC when the microcatheter was advanced within 2 cm of a lesion or when percutaneous puncture was performed. There were two transient complications: one increase in a preexisting fifth nerve palsy and one increase in preexisting hemiparesis.

CONCLUSION: EVAC is a promising liquid embolic material providing long-term occlusion of blood vessels.

Gobin YP, Murayama Y, Milanese W, Chow K, Gonzalez NR, Duckwiler GR, Vinuela F. Head and Neck Hypervascular Lesions: Embolization with Ethylene Vinyl Alcohol Copolymer – Laboratory Evaluation in Swine and Clinical Evaluation in Humans. Radiology, 11-02:309-317

10.16.8. Treatment of Pelvic Arteriovenous Malformations with Ethylene Vinyl Alcohol copolymer (Onyx)

OBJECTIVE: Case studies of two patients treated with ethylene vinyl alcohol, a radiopaque, non-adhesive liquid casting agent, are reported.

METHODS AND MATERIALS: Both patients presented with large symptomatic pelvic AVMs requiring therapy. Coaxial microcatheter techniques were used to deliver the liquid embolic agent.

RESULTS: Two successful embolizations of large pelvic arteriovenous malformations (AVMs) were done to achieve complete clinical success in one case and partial success in the other. Clinical success has been maintained in both patients at 2-year follow-up.

Castaneda F. Goodwin SC, Swischuk JL, Wong GC, Bonilla SM, Wang MJ, Treatment of Pelvic Arteriovenous Malformations with Ethylene Vinyl Alcohol copolymer (Onyx). J Vascular Interventional Radiology 2002 May; 13 (5): 513-6.

10.16.9. A New Liquid Embolic Material for Liver Tumors

OBJECTIVE: The authors evaluated the feasibility of a new liquid embolic material, Onyx, for treating liver tumors.

MATERIAL AND METHODS: Onyx is a mixture of 6% (w/v) ethylene-vinyl-alcohol copolymer dissolved in anhydrous dimethyl sulfoxide (DMSO) with 28% (w/v) tantalum

powder. In addition to 6% Onyx, we also tried 4%, 2% and 1% solutions, prepared by adjusting the amount of DMSO. We used 15 white rabbits with liver tumors created by percutaneous injection of VX2 tumor cells. In 4 groups with 3 rabbits in each, the liver arteries were embolized with 6%, 4%, 2% and 1% Onyx, respectively, and in 3 rabbits DMSO alone was injected. The injections were performed just proximal to the bifurcation of the proper hepatic artery, followed by celiac arteriography. Post mortem, the livers were examined by soft-tissue radiography, and liver-tissue section microscopy.

RESULTS: The maximum number of arterial branching points passed by embolic material in either the right or left hepatic arteries was 11, 15 and 16, for 6%, 4% and 2% Onyx, respectively, but was non-measurable for 1% Onyx. Minimum diameters of arteries reached by 6%, 4%, 2% and 1% Onyx in tumorous areas were 40 micron, 35 micron, 20 micron and 10 micron, respectively, and in non-tumorous areas 35 micron, 5 micron, 5 micron and 5 micron, respectively.

CONCLUSION: This study suggests that Onyx may be feasible for treatment of hepatic tumors.

Komemushi A, Tanigawa N, Okuda Y, Kojima H, Fijii H, Shomura Y, Sougawa M, Sawada S. A New Liquid Embolic Material for Liver Tumors. Acta Radiology 2002 March; 43 (2): 186-91.

10.16.10. Surgical handling characteristics of an ethylene vinyl alcohol copolymer compared with N-butyl cyanoacrylate used for embolization of vessels in an arteriovenous malformation resection model in swine

OBJECTIVE: There have been significant improvements in neurovascular technology and implants over the past decade. One such material, N-butyl cyanoacrylate (NBCA), is now commercially available for cerebral arteriovenous malformation (AVM) embolization in the US. An ethylene vinyl alcohol copolymer preparation, Onyx, winch is currently being evaluated, is approved for use outside North America. Although reports indicate that Onyx may be superior to NBCA from an endovascular perspective, little information exists about its surgical handling characteristics. The purpose of this study was to compare the surgical handling characteristics of Onyx-treated vessels with those of NBCA-embolized vessels in an AVM resection model.

METHODS: Fourteen pigs (two groups of seven) were anesthetized. A femoral artery was cannulated, followed by selective catheterization of the ascending pharyngeal arteries. Nidal rete mirabile (RM) embolizations were performed using either 6% Onyx or 20% NBCA. After angiographically confirmed obliteration of flow in the right RM, microsurgical resection of this structure was performed. Surgical handling characteristics of the embolized RM were rated on a scale of I to 5 and blood loss was recorded. Different surgeons performed the embolizations and resections. The surgeon who performed resections was blinded to the embolization agent used, and the data analysis was also performed in a blinded fashion. The surgical handling scores were superior ($p < 0.05$) in the Onyx-treated group. Although there was also less blood loss in this group, the difference was not significant.

CONCLUSIONS: Onyx, which may offer endovascular advantages, also seems to provide benefits for the surgeon. Subjectively, the surgeon who performed the resections believed that Onyx was softer and handled better than NBCA.

Akin ED, Perkins E, Ross IB, Surgical handling characteristics of an ethylene vinyl alcohol copolymer compared with N-butyl cyanoacrylate used for embolization of vessels in an arteriovenous malformation resection model in swine. J Neurosurgery, 366-370, 2003.

10.16.11. N-Butyl Cyanoacrylate Embolization of Cerebral Arteriovenous: Results of a Prospective, Randomized, Multi-center Trial.

BACKGROUND AND PURPOSE: Liquid N-butyl cyanoacrylate (n-BCA) use for the treatment of arteriovenous malformations (AVM) in the brain has become part of medial practice. However, no study has led to the Food and Drug Administration's approval of n-BCA for intravascular use. The purpose of this study was to verify the effectiveness and safety of an n-BCA/Tantalum Powder/Ethiodized Oil mixture, compared with conventional treatment (Trufill polyvinyl alcohol (PVA) for preoperative embolization of cerebral AVM.

METHODS*:* Between October 15, 1996, and March 24, 1999, 104 patients at 13 centers were prospectively randomized to undergo embolization using an n-BCA/Tantalum Powder/Ethiodol mixture of Trufill PVA. The pre-embolization therapy goals were determined in terms of the number of pedicles to be embolized and the percent of nidus reduction expected. Embolization results were evaluated by a central laboratory. Subsequent surgical resection data were recorded. Safety evaluation data included recording device complications, procedure complications, and intracranial events/overall neurologic outcomes, which could be either device-related, procedure-related, or both.

RESULTS*:* The reduction of AVM dimensions (79.4% in the n-BCA group and 86.9% in the PVA group) and the mean number of vessels embolized (2.2 in the n-BCA group and 2.1 in the PVA group) was similar in the two groups. Coils were used more commonly with PVA embolization ($P < .0001$). No difference were detected in surgical resection time, number of patients who required transfusion, volume and number of transfusion units, or type and volume of fluid replacement. Glasgow Outcome Scale scores were not significantly different between the two groups before treatment, after embolization, or after resection. Two of 42 patients who underwent resection and had been treated with n-BCA experienced post-resection hematoma, compared with eight of 45 patients who underwent resection and had been treated PVA ($P < .05$).

CONCLUSION*:* This prospective, randomized trial showed that n-BCA is equivalent to PVA as a preoperative embolic agent for treatment of cerebral AVM as determined by percent of nidus reduction and number of feeding pedicles embolized.

The n-BCA Trial Investigators. N-Butyl Cyanoacrylate Embolization of Cerebral Arteriovenous: Results of a Prospective, Randomized, Multi-center Trial. American Journal of Neuroradiology 23:74a8-755, May 2002

10.17.Bibliography

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11. LABELING – INSTRUCTIONS FOR USE

Micro Therapeutics, Inc.

Onyx® Liquid Embolic System

INSTRUCTIONS FOR USE

US05830178, US05785642, US05755658, US05695480, US05667767, US05958444 and Other US and Foreign Patents Pending

CAUTION

?? ~~Investigational device. Limited by Federal (U.S.) law to investigational use.~~

?? Performing embolization to occlude blood vessels is a high risk procedure. This device should be used only by physicians with neurointerventional training and a thorough knowledge of the pathology to be treated, angiographic techniques, and super-selective embolization.

It is important to read the instructions for use with careful attention to warnings prior to using this product.

Onyx and DMSO are sterile (dry heat) and non-pyrogenic.

Syringes are sterile and non-pyrogenic.

This device is intended for SINGLE USE ONLY. DO NOT RESTERILIZE AND/OR REUSE.

DESCRIPTION

Onyx® is a non-adhesive liquid embolic agent comprised of EVOH (ethylene vinyl alcohol) copolymer dissolved in DMSO (dimethyl sulfoxide), and suspended micronized tantalum powder to provide contrast for visualization under fluoroscopy. The Onyx Liquid Embolic System (LES™) consists of a 1.5 ml vial of Onyx, a 1.5 ml vial of DMSO, and three 1 ml Onyx delivery syringes. A DMSO compatible delivery micro catheter that is indicated for use in the neuro vasculature (e.g. Rebar™ or UltraFlow™ HPC catheters) is used to access the embolization site.

INDICATIONS FOR USE

Presurgical embolization of brain arteriovenous malformations (AVMs).

CONTRAINDICATIONS

Not for use with premature infants (<1,500 g) or individuals with significant liver function impairment.

POTENTIAL COMPLICATIONS

Potential complications include, but are not limited to:

Stroke	Hearing problems
Motor deficits	Hemorrhage
Paresis or paralysis	Seizures
Numbness	Dizziness
Speech deficits	Brain edema
Sensory problems	Death

PRINCIPLE OF OPERATION

Onyx is delivered through a micro catheter into the AVM under fluoroscopic control. The DMSO solvent dissipates into the blood and interstitial fluids, causing the EVOH copolymer and suspended tantalum to precipitate *in situ* into a spongy, coherent embolus. Onyx immediately forms a skin as the polymeric embolus solidifies from the outside to the inside, while traveling more distally in the vessel. Since Onyx is non-adhesive, the micro catheter can be left in place while slow, controlled injections are performed. Post embolization angiography can be conducted with the delivery micro catheter in place, enabling the physician to make additional injections through the same micro catheter, if necessary.

PRODUCT CONFIGURATIONS

Onyx is available in two product formulations, Onyx-18 (6% EVOH) and Onyx-34 (8% EVOH).

- Onyx-18 (nominal viscosity of 18 cSt at 40°C): Recommended when feeding pedicle injections will be conducted close to the nidus, and the flow rate is less than 50 ml/min.
- Onyx-34 (nominal viscosity of 33 cSt at 40°C): Recommended when feeding pedicle injections will be conducted close to the nidus, at flow rates up to 200 ml/min, and in 3 mm or smaller diameter vessels.

Onyx-18 will travel more distally and penetrate deeper into the nidus due to its lower viscosity compared to Onyx-34. Final solidification occurs within five minutes for both product formulations.

STORAGE

Store Onyx and DMSO between -20? and 55?C. Prior to use, maintain product temperature between 19? and 24?C. If product freezes due to exposure to colder temperatures, thaw at room temperature before use.

WARNING

Inspect product packaging prior to use. Do not use if sterile barrier is open or damaged.

DIRECTIONS FOR USE

WARNING: Verify that adequate sedation is used throughout the embolization procedure. Insufficient sedation may result in patient discomfort or movement. Patient movement during embolic agent injection may result in embolization of an unintended vessel.

NOTE: Adjunctive coil use should be considered if angiography shows that venous drainage of the AVM appears almost simultaneously with arterial opacification. Based on results from *in vitro* and *in vivo* testing, coil placement prior to Onyx injection should be considered for feeding pedicles with AV fistulae having flow rates exceeding 200 ml/min and vessel diameters of 3 mm or greater.

1. Shake Onyx at least 20 minutes on an Onyx mixer[20] at a setting of 8. Continue mixing until ready to inject Onyx per step 5.

   WARNING: Failure to continuously mix Onyx for the required time may result in inadequate suspension of the tantalum, resulting in inadequate fluoroscopic visualization during delivery.

2. Confirm micro catheter placement with injection of contrast agent per institutional procedure.

   WARNING: Use only MTI micro catheters. Other micro catheters may not be compatible with DMSO and their use can result in thromboembolic events due to catheter degradation.

3. Flush contrast from micro catheter with 10 ml of saline. Leave the syringe connected.

4. Filling catheter deadspace: aspirate approximately 0.8 ml of MTI DMSO into the yellow MTI 1 ml DMSO syringe. Inject DMSO into delivery micro catheter in sufficient volume to fill catheter deadspace. Refer to delivery catheter labeling for deadspace volume.

   WARNING: Use only the MTI 1 ml syringe to inject DMSO and Onyx. Other syringes may not be compatible with DMSO.

5. Ensure that Onyx has been mixed per step 1. Fill white MTI 1 ml syringe with Onyx through an 18 or 20 gauge needle. As soon as the DMSO has been injected into the catheter deadspace, remove the DMSO syringe, hold the catheter hub in a vertical position, and overfill and wash the luer hub with the balance of the DMSO.

6. ***Immediately*** connect the Onyx syringe to the hub, making sure there is no air in the hub during the connection. For optimal fluoroscopic visualization, quickly point the syringe vertically to create an interface between the DMSO and the Onyx.

   WARNING: Premature solidification of Onyx may occur if micro catheter luer contacts saline, blood or contrast of any amount.

7. While holding the syringe vertically, begin injecting Onyx to displace DMSO. Based on clinical practice, it is recommended that Onyx be injected at a slow, steady rate of 0.16 ml/min (0.25 ml/90 sec). Do not exceed 0.3 ml/min.

   WARNINGS: Inject Onyx immediately after mixing. If Onyx injection is delayed, tantalum settling can occur within the syringe resulting in poor visualization of Onyx during injection.

   Do not exceed 0.3 ml/min injection rate. Animal studies have shown that rapid injection of DMSO into the vasculature may lead to vasospasm and/or angionecrosis.

   Only use thumb pressure to inject Onyx. Using palm of hand to advance plunger may result in catheter rupture due to overpressurization in the event of catheter occlusion.

   Adequate fluoroscopic visualization must be maintained during Onyx delivery or non-target vessel embolization may result. If visualization is lost at any time during the embolization procedure, HALT Onyx delivery until adequate visualization is re-established.

8. Continue holding syringe vertically until Onyx passes through the catheter hub. Once Onyx passes through the hub, hold syringe in a more comfortable position and continue injecting Onyx at the slow, steady, recommended rate of 0.16 ml/min. Monitor volume injected to correspond to volume of vascular space being filled.

   WARNINGS: Do not allow more than 1 cm of Onyx to reflux back over catheter tip. Excessive Onyx reflux may result in difficult catheter removal.

[20] Scientific Industries Genie 2, Model No. 120V SI-0240, Vial Attachment No. OA- 0570-010

After using a micro catheter with Onyx, do not attempt to clear or inject any material through it. Such attempts may lead to embolus or embolization of an unintended area.

STOP injection if Onyx is not visualized exiting catheter tip. If the catheter becomes occluded, over-pressurization can occur. During Onyx injection, continuously verify that Onyx is exiting the catheter tip. Testing has shown that over-pressurization and rupture can occur if 0.05 ml of Onyx is injected and is not visualized exiting the catheter tip.

STOP injection if increased resistance to Onyx injection is observed. If increased resistance occurs, determine the cause (e.g., Onyx occlusion in catheter lumen) and replace the catheter. Do not attempt to clear or overcome resistance by applying increased injection pressure, as use of excessive pressure may result in catheter rupture and embolization of unintended areas.

DO NOT interrupt Onyx injection for longer than two minutes prior to re-injection. Solidification of Onyx may occur at the catheter tip resulting in catheter occlusion, and use of excessive pressure to clear the catheter may result in catheter rupture.

9. Upon completion of Onyx injection, wait a few seconds, slightly aspirate syringe, and then gently pull the catheter to separate it from the Onyx cast.

PRECAUTIONS

Failure to wait a few seconds to retrieve the micro catheter after Onyx injection may result in fragmentation of Onyx into non-target vessels.

Difficult catheter removal or catheter entrapment may be caused by any of the following:

- Angioarchitecture: very distal AVM fed by afferent, lengthened, and tortuous pedicles
- Vasospasm
- Reflux

Should catheter removal become difficult, the following will assist in catheter retrieval:

- Carefully pull the catheter to assess any resistance to removal.
- If resistance is felt, remove any "slack" in the catheter.
- Gently apply traction to the catheter (approximately 3-4 cm of stretch to the catheter).
- Hold this traction for a few seconds and release. Assess traction on vasculature to minimize risk of hemorrhage.
- This process can be repeated intermittently until catheter is retrieved.

For entrapped catheters:

- Under some difficult clinical situations, rather than risk rupturing the malformation and consequent hemorrhagic complications by applying too much traction on an entrapped catheter, it may be safer to leave the micro catheter in the vascular system.
- This is accomplished by stretching the catheter and cutting the shaft near the entry point of vascular access allowing the catheter to remain in the artery.
- If the catheter breaks during removal, distal migration or coiling of the catheter may occur. Same day surgical resection should be considered to minimize the risk of thrombosis.

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12. PHYSICIAN TRAINING PROGRAM

(---------- Data Redacted ----------)